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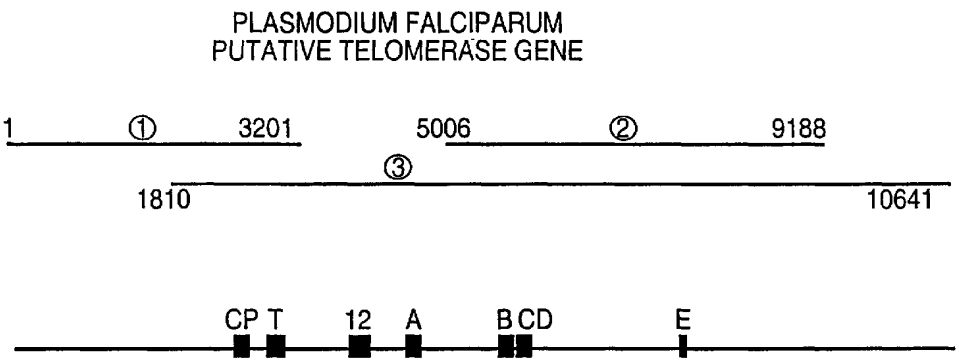
(54) Title: TELOMERASE REVERSE TRANSCRIPTASE (TERT) GENES



① SANGER CENTRE CHROMOSOME 13 CONTIG 41294

② SANGER CENTRE CHROMOSOME 13 CONTIG 02431

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(57) Abstract: The present invention pertains, in general, to the identification, isolation and use of Telomerase Reverse Transcriptase (TERT) genes and the proteins encoded by such genes. In particular, the present invention pertains to the identification, isolation and use of TERT genes and TERT proteins from several genetically diverse and economically important organisms, including two human pathogens and an agronomic crop species.

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TELOMERASE REVERSE TRANSCRIPTASE (TERT) GENES

FIELD OF THE INVENTION

The present invention pertain s, in general, to the identification and use of Telomerase Reverse Transcriptase (TERT) genes and the proteins encoded by such genes. In particular, the present invention pertains to the identification and use of TERT genes and TERT proteins from several genetically diverse and economically important organisms, including two human pathogens and an agronomic crop species.

BACKGROUND OF THE INVENTION

All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

TERT genes have been identified in mammals (mouse and human), yeasts (*Saccharomyces cerevisiae, Schizosaccharomyces pombe*) and ciliated protozoans *(Tetrahymena thermophila, Oxytricha trifallax and Euplotes aediculatus*) (Ligner, J. *et al.*, 1997; Bryan, T.M. *et al.*, 1998; Nakamura, T.M. *at al.*, 1997; Greenberg, R.A. *et al.*, 1999). Telomerase RNA has been cloned from bovine testis (Tsao *et al.*, 1998) and from approximately twenty other organisms.

The protein encoded by the TERT gene, together with an RNA subunit, comprise telomerase, an enzyme required for the maintenance of telomeres. Telomeres, which are long stretches of short DNA sequence repeats located on the ends of linear chromosomes, are an essential component of the eukaryotic genome. They serve as "caps" on chromosomal termini, preventing loss of terminal sequence information and degradation of chromosomal DNA, as well as regulating expression of nearby genes. Telomerase has been shown to be responsible for maintenance of telomere length, as cells lacking this enzyme experience a shortening and eventual loss of telomeric sequence. For a recent

review, *see* Bryan and Cech, 1999.

Telomere length and telomerase activity have been implicated in studies of both aging and cancer. Telomeres are believed to function as a molecular clock, gradually shortening as a cell ages and signaling cell death when the telomeres decay down to a critical length. It has been observed that in many immortal cells, telomerase appears to be overactive, resulting in telomeres that are maintained indefinitely. These observations have led to great interest in research programs attempting to develop pharmaceuticals that either ameliorate or activate telomerase activity, as well as diagnostic tools to detect telomerase activity. For reviews, *see* Raymond, 1996 and Holt and Shay, 1999.

We have identified TERT genes from three economically important and genetically diverse organisms: *Plasmodium falciparum, Candida albicans and Oryza sativa*. *P. falciparum* and *C. albicans* are the causative agents of serious medical conditions of humans while *O. sativa* is food staple of people throughout the world, especially those of third world countries. The discovery of these genes will have a profound effect on our ability to genetically manipulate and control the growth of these important organisms.

SUMMARY OF THE INVENTION

This invention comprises compositions and methods for the identification and use of novel TERT genes. In particular, this invention provides comprises compositions and methods for the identification and use of TERT genes of *Plasmodium falciparum, Candida albicans* and *Oryza sativa*.

The present invention provides isolated nucleic acid molecules coding for TERT genes and TERT gene fragments wherein the isolated nucleic acid molecules include: (a) isolated nucleic acid molecules that encode the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (b) isolated nucleic acid molecules that encode a fragment of at least 6 amino acids of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (c) isolated nucleic acid molecules which hybridize to the complement of a nucleic acid molecule comprising SEQ

ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9 under conditions of sufficient stringency to produce a clear signal; and (d) isolated nucleic acid molecules which hybridize to a nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 under conditions of sufficient stringency to produce a clear signal. In particular, this invention provides nucleic acid molecules with the nucleic acid sequences of SEQ ID NO. 1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 and SEQ ID NO.9.

This invention also provides such isolated nucleic acid molecules coding for TERT genes or gene fragments operably linked to one or more expression control elements.

This invention also provides vectors comprising such isolated nucleic acid molecules coding for TERT genes and TERT gene fragments.

This invention also provides host cells, tissues, organs and organisms transformed to contain such nucleic acid molecules coding for TERT genes and TERT gene fragments. This invention further provides host cells, tissues, organs and organisms comprising vectors comprising such isolated nucleic acid molecules coding for TERT genes and TERT gene fragments.

This invention also provides methods for producing a polypeptide comprising the step of culturing a host cell transformed with such nucleic acid molecules coding for TERT genes and gene fragments under conditions in which the protein encoded by these nucleic acid molecules are expressed. This invention further provides isolated polypeptides produced by such methods.

This invention also provides isolated TERT polypeptides and TERT polypeptide fragments wherein the polypeptides include: (a) those coded by the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (b) those comprising a fragment of at least 6 amino acids of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (c) conservative amino acid substitutions of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; and (d) naturally occurring amino acid sequence variants of SEQ ID NO.2, SEQ

ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

The invention also provides isolated antibodies that bind to such TERT polypeptides and TERT polypeptide fragments. The invention further provides such antibodies wherein the antibodies are monoclonal or polyclonal antibodies.

The invention also provides methods of identifying an agents which modulate the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the steps of:

exposing cells which express the nucleic acid to the agent; and

determining whether the agent modulates expression of said nucleic acid, thereby identifying an agent which modulates the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

The invention also provides methods of identifying agents which modulate at least one activity of a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the steps of:

exposing cells which express the protein to the agent;

determining whether the agent modulates at least one activity of said protein, thereby identifying an agent which modulates at least one activity of a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

The invention also provides methods of identifying binding partners for a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10, comprising the steps of:

exposing said protein to a potential binding partner; and

determining if the potential binding partner binds to said protein, thereby identifying binding partners for a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

The invention also provides methods of modulating the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID

NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the step of:

administering an effective amount of an agent which modulates the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

This invention also provides methods of modulating at least one activity of a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the step of:

administering an effective amount of an agent which modulates at least one activity of a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

This invention also provides methods for diagnosing *Plasmodium falciparum* infection in a patient comprising the steps of:

obtaining a cell sample from the patient;

determining whether the nucleic acid of SEQ ID NO.5 or SEQ ID NO.7 or the protein of SEQ ID NO.6 or SEQ ID NO.8 is present within the cell sample; and

correlating the presence of the nucleic acid of SEQ ID NO.5 or SEQ ID NO.7 or the protein of SEQ ID NO.6 or SEQ ID NO.8 with the presence of *Plasmodium falciparum*.

This invention also provides methods for diagnosing *Candida albicans* infection in a patient comprising the steps of:

obtaining a cell sample from the patient;

determining whether the nucleic acid of SEQ ID NO.1 or SEQ ID NO.3 or the protein of SEQ ID NO.2 or SEQ ID NO.4 is present within the cell sample; and

correlating the presence of the nucleic acid of SEQ ID NO.1 or SEQ ID NO.3 or the protein of SEQ ID NO.2 or SEQ ID NO.4 with the presence of *Candida albicans*.

One skilled in the art can easily make any necessary adjustments in accordance with the necessities of the particular situation.

Further objects and advantages of the present invention will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Identification of the TERT gene for *P. falciparum*.

① Sanger Centre chromosome 13 contig 41294.

② Sanger Centre chromosome 13 contig 02431.

③ TIGR Database chromosome 14 contig 5560 (now #364).

④ *P. falciparum* Putative Telomerase Gene. Letters indicate motifs.

Figure 2. Sequence alignment of the *P. falciparum* TERT gene and the TERT genes of other organisms. Organism codes are as follows:

h. = Human, SEQ ID NO:40

m. = Mouse, SEQ ID NO:41

o. = *Oxytricha trifallax,* SEQ ID NO:42

E. = *Euplotes aediculatus,* SEQ ID NO:43

T. = *Tetrahymena thermophila,* SEQ ID NO:44

Sp. = *Schizosaccharomyces pombe,* SEQ ID NO:45

Sc. = *Saccharomyces cerevisiae,* SEQ ID NO:46

Ca. = *Candida albicans*. The consensus sequence (SEQ ID NO:47) appears as the last line in this set of compared sequences.

Figure 3. TERT RT-PCR on Total RNA of *P. falciparum*.

M 1kb ladder (Promega®).

Lane 1 RT-PCR of 4µg *P. falciparum* total RNA with primers pfRT and pfTELfor (45 min at 48C followed by 40 cycles of 1 min at 94C, 1 min at 52C, 4 min

at 68C), followed by nested PCR of 3 µl product with primers pfBREV and pfTELfor (20 cycles of 1min at 94C, 1 min at 52C, 4 min at 68C). 25 µl product electrophoresed on 0.8% agarose gel. Arrow indicates signal for TERT mRNA.

Lane 2 No AMV-reverse transcriptase control. All other conditions same as Lane 1.

Lane 3 No template control. All other conditions same as Lane 1.

Lane 4 RT-PCR of 4µg *P. falciparum* total RNA with pfRT2 and pf2160, followed by nested PCR with primers pfREV2 and pf2160. 10µl product electrophoresed on 0.8% agarose gel.

Lane 5 No AMV-reverse transcriptase control. All other conditions same as Lane 4.

Lane 6 No template control. All other conditions same as Lane 4.

Figure 4. TERT RT-PCR Gel on Total RNA of *C. albicans*.

Lane 1 RT PCR on 5 µg *Candida albicans* total RNA with primers CaFor2 and CaRT2 (45 min at 48C followed by 40 cycles of 1min at 94C, 1 min at 52C, 2 min at 68C). Nested PCR of 3 µl product (20 cycles of 1min at 94C, 1 min at 52C, 4 min at 68C) with primers CaFor2 and CaNest2. 1 µl sample loaded on 0.8% agarose gel.

Lane 2 No AMV-reverse transcriptase control. All other conditions as in Lane 1.

Lane 3 No template control. All other conditions as in Lane 1.

Lane 4 RT PCR on 0.85µg *Candida albicans* total RNA with primers CaRT3 and CaFor3 (45 min at 48C followed by 40 cycles of 1min at 94C, 1 min at 52C, 2 min at 68C). 10 µl product electrophoresed on 0.8% agarose gel.

Lane 5 No AMV-reverse transcriptase control. All other conditions as in Lane 4.

Lane 6 No template control. All other conditions as in Lane 4.

Figure 5. TERT RT-PCR Gel on Total RNA of *C. albicans*.

Product 1 (P1) was amplified with RT3 and FOR1; product 2 (P2) with RT1 and FOR2; product 3 (P3) with RT2 and FOR2; and product 4 (P4) with RT3 and FOR3.

Products 2 and 4 were not visible on agarose gel after 40 cycles, and 3 µl PCR product was reamplified with NEST1 and FOR2 (P2) or NEST2 and FOR2 (P4) for another 12 cycles of PCR as described for Figure 4.

Figure 6. Sequence alignment of the *O. sativa* TERT gene and the *Arabidopsis thaliana* (SEQ ID NO:48) TERT genes.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

Definitions.

"Allele" or "allelomorph" refers to any of the forms of the same gene that occur at the same locus on a homologous chromosome but differ in base sequence. Two or more alleles are said to be allelic or allelomorphic to each other, and if more than two alleles exist in a population, the locus is said to show multiple allelism.

"Apoptosis" refers to cell death that may occur by accident, cell necrosis, or by an intracellular controlled process characterized by a condensation and, subsequent, fragmentation of the cell nucleus during which the plasma membrane remains intact.

"Modulate" refers to the inhibition, induction, agonism and/or antagonism of the expression or function of a TERT gene or TERT gene product.

"Nucleic acid" includes DNA and RNA molecules and is used synonymously with the terms "nucleic acid sequence" and "polynucleotide."

"Polypeptide" refers to an amino acid sequence including, but not limited to, proteins and protein fragments, naturally derived or synthetically produced.

"Senescence" refers to the process of growing old or aging.

"Telomerase" refers to a ribonucleoprotein, telomere specific reverse transcriptase, which contains some protein components and telomerase RNA components. Telomerase can synthesize the tandem repeat units of telomere to the 3' end of telomeric primers without a template. The RNA component of the enzyme contains the complementary sequence of the telomeric repeats it synthesizes.

"Telomere-specific repeats" refers to simple DNA repeat sequences found at the ends of chromosomes. These sequences are sometimes referred to as "telomeric DNA" by those skilled in the art.

"Telomerase enzyme subunit" refers to any domain, or region or discrete part of a polypeptide sequence that can be equated with telomerase enzyme function.

"Telomere" refers to the specialized DNA sequence found at the end of the chromosome that provides stability to the chromosome, prevents fusion with other natural or broken ends, and allows replication without loss.

"TERT" refers to Telomerase Reverse Transcriptase. TERT, as it is used herein, can refer to either the gene encoding the enzyme or to the enzyme (*i.e.*, protein) itself. TERT refers to the nucleoprotein, or enzyme, portion of telomerase. TERT genes have also been called "Ever Shorter Telomeres" or "EST" genes.

"Transcriptional factors" refers to a class of proteins that bind to a promoter or to a nearby sequence of DNA to facilitate or prevent transcription initiation.

"Transcriptional profiling" refers to any assay method or technique which is capable of analyzing, quantitatively and/or qualitatively, one or more mRNA species found in a cell or a nucleic acid sample. For example, such assays include, but are not limited to, RT-PCR, quantitative PCR (Q-PCR), RNase protection assays, subtractive hybridization, READS and Northern blots.

Overview of the Invention

The present invention is based in part on the identification of new TERT genes and the TERT proteins encoded by these genes found in three economically important organisms.

The newly identified TERT proteins can serve as targets for agents that can be used to modulate the expression or activity of the enzyme. For example, agents may be identified which modulate biological processes associated with telomerase, such as but not limited to: the maintenance of telomeres, replicative senescence, cell multiplication, mitotic clock functioning, aging, proliferative capacity, tumorigenesis, tumor progression, cellular immortilization, cellular senescence, apoptosis and cell death.

Agents identified by the methods of the present invention can inhibit or promote the growth of specific organisms by modulating the expression or activity of the TERT proteins specific to the organisms. Thus, agents can be identified which are useful in the prevention, treatment or eradication of infection by pathogens, including infection by parasitic protozoans and pathogenic yeasts. Agents may also be identified which modulate the biological processes associated with recovery from various types of cancer.

Agents identified by the methods of the present invention can modulate the biological processes of plants, thereby controlling plant growth ability and rate. The agents identified by the methods of the present invention can be used in various agricultural chemicals, including growth regulators, herbicides and fertilizers.

The present invention is further based on the development of methods for isolating binding partners that bind to the TERT proteins. Probes based on the proteins are used as capture probes to isolate potential binding partners, such as other proteins. Dominant negative proteins, DNAs encoding these proteins, antibodies to these proteins, peptide fragments of these proteins or mimics of these proteins may be introduced into cells to affect function. Additionally, these proteins provide a novel target for screening of synthetic small molecules and combinatorial or naturally occurring compound libraries to discover novel therapeutics to regulate various cellular processes or diseases such as cell cycle, cell death and tumor progression.

Plasmodium falciparum TERT Gene and TERT Protein.

We have identified a TERT gene from the parasite *Plasmodium falciparum* and performed experiments that indicate that the TERT gene product is expressed *in vivo*. This is the first identification of this essential gene and protein in this important human pathogen.

P. falciparum is a protozoan which is the causative agent of malaria, Malaria is the world's most important tropical parasitic disease, presenting 300-500 million clinical cases per year and causing over 1 million deaths per year (WHO, 1998). Thus, identification of the TERT gene product from *Plasmodium,* which is a vital component of cell viability, is an important contribution to research towards eradication of this disease.

Our discovery of the TERT gene and TERT protein of *Plasmodium falciparum* makes possible avenues of research aimed at understanding the structure and function of the TERT gene and its effects on the *Plasmodium* life cycle and pathogenicity. Possible utility includes but is not limited to development of natural or artificial compounds that affect TERT activity, or screening procedures to aid in detection of this pathogen.

Candida albicans TERT Genes and TERT Proteins .

We have identified TERT genes and TERT proteins from the yeast *Candida albicans*, and performed experiments that indicate that the TERT gene product is expressed *in vivo*. This is the first identification of these essential genes and proteins in this important human pathogen. The *C. albicans* proteins are the smallest TERT homologues discovered to date. Their compact size makes them an attractive target for gene analysis and for protein crystallization.

C. albicans is the cause of vaginal candidiasis (commonly known as yeast infections) in women. Additionally, *Candida* can cause severe, life threatening infections in the respiratory tract and major organs of immunocompromised patients, such as persons suffering from HIV disease, patients undergoing immunosuppresive therapy or the elderly (McCullough *et al.*, 1996). Thus, identification of the TERT genes and TERT proteins from *Candida*, which is a vital component of cell viability, is an important contribution to research towards eradication of disease caused by this pathogen.

Our discovery of the TERT genes and TERT proteins of *Candida albicans* makes possible avenues of research aimed at understanding the structure and function of the TERT genes and its effects on the *C. albicans* life cycle and pathogenicity. Possible utility includes but is not limited to development of natural or artificial compounds that affect TERT activity, or screening procedures to aid in detection of this pathogen.

The National Institutes of Health is currently researching fungal virulence genes using a gene disruption approach. At least four *C. albicans* genes involved in human pathogenicity have been identified by this method to date (Kwon-Chun, 1998). The identification of the TERT genes thus makes possible studies to determine the effects of these genes on the pathogenicity of the organism. Similar studies of the function of the TERT gene/catalytic subunit of the TERT protein have been carried out in the ciliate *Euplotes aediculatus* and in the fission yeast *Schizosaccharomyces pombe* (Nakamura *et al.*, 1997).

Oryza sativa TERT Gene Fragment and TERT Protein Fragment

We have identified a TERT gene fragment and TERT protein fragment from rice, *Oryza sativa*. This is the first identification of a fragment of this essential gene in an important crop plant.

Our discovery of the TERT gene fragment of *O. sativa* makes possible avenues of research aimed at understanding the structure and function of the TERT gene and its effects on the life cycle of the rice plant. Potential interest in this discovery include implications for plant cell proliferative capacity by, for example, by down-regulating telomerase expression (*i.e.*, prevent growth of roots and flowers in weeds) or by up-regulating telomerase expression leading to a larger endosperm and thus improved grain yield.

Telomeres and Telomerase

Telomeres

A large fraction of the deoxyribonucleic acid (DNA) of most higher eukaryotes is made up of repeat sequences ranging from a few copies up to millions of copies. Repeat

functional sequences occur at the telomeres and centromeres of eukaryotic chromosomes.

Telomeres are specialized DNA sequences found at the ends of the chromosomes of eukaryotes which function in chromosome protection, positioning, and replication. Telomeres protect linear chromosomes from degradation and fusion to other chromosomes, and are thought to be a site of attachment to the nuclear matrix at times during the cell cycle. As chromosome caps they reduce the formation of damaged and rearranged chromosomes which arise as a consequence of recombination-mediated chromosome fusion events.

Generally, telomeres consist of tens to thousands of tandem repeats of a telomere motif sequence and associated proteins. The telomeres from all species show the same pattern: a short DNA sequence, one strand G-rich and one C-rich, that is tandemly repeated many times. The repeating telomeric unit found in *Tetrahymena* is T_2G_4, in the ciliated protozoan *Oxytricha* it is T_4G_4, and in *Saccharomyces cerevisiae* it is $T_{1\text{-}3}G_{1\text{-}3}$. In humans and other mammals this motif is 5'-d(TTAGGG)-3'. Sequences specific to other species such as plants may be found in Greider *et al.* (1990).

Telomeres of all human chromosomes are composed of variable length arrays of the TTAGGG repeat units with the G-rich strand oriented 5' to 3' towards the telomere. Variant telomere repeat units such as TTGGGG and TGAGGG have been identified but tend to be located at the proximal ends of human telomeres. Methods for detecting and quantitating multiple copies of a repeat sequence, such as a telomere (or centromere) repeat sequence, are provided in WO 97/14026. Methods for characterizing variability in telomere DNA by Polymerase Chain Reaction (PCR) are provided in WO 96/12821.

Telomerase

The maintenance of telomeres is required for cells to avoid replicative senescence and to continue to multiply. Chromosomes lose about 50-200 nucleotides of telomeric sequence from their ends per cell division, and the shortening of telomeres may act as a mitotic clock shortening with age both *in vitro* and *in vivo* in a replication dependent manner (Harley, 1991). Telomeric sequences can be added back to the chromosome ends, by telomere terminal transferase, also known as telomerase enzyme or simply as

telomerase. Methods and compositions for increasing telomere length in normal cells to increase the proliferative capacity of cells and to delay the onset of senescence are provided in U.S. Patent Number 5,686,306.

Telomerase is a ribonucleoprotein enzyme that elongates the G-rich strand of chromosomal termini by adding telomeric repeats. This elongation occurs by reverse transcription of a part of the telomerase RNA component, which contains a sequence complementary to the telomere repeat. Following telomerase-catalyzed extension of the G-rich strand, the complementary DNA strand of the telomere is presumably replicated by more conventional means.

Telomerase is a reverse transcriptase composed of both ribonucleotide acid (RNA) and protein, wherein the RNA molecule functions as the template for the telomeric repeat. The RNA moiety of human telomerase contains the 5'-CCCTAA-3' sequence that may act as the template for *de novo* synthesis. The enzyme also contains a region that recognizes the guanine rich single strands of a DNA substrate. Methods and compositions for the determination of telomere length and telomerase activity are provided in U.S. Patent Numbers 5,489,508 and 5,707,795.

The RNA component of the telomerase enzymes of *Saccharomyces cerevisiae*, certain species of *Tetrahymena*, as well as that of other ciliates, such as *Euplotes* and *Glaucoma*, has been sequenced and reported in the scientific literature. See Singer and Gottschling, 21 Oct. 1994, Science 266:404-409; Lingner et al., 1994, Genes & Development 8:1984-1988; Greider and Blackburn, 1989, Nature 337:331-337; Romero and Blackburn, 1991, Cell 67:343-353; and Shippen-Lentz and Blackburn, 1990, Science 247:546-552; and U.S. Patent No. 5,698,686, each of which is incorporated herein by reference.

The telomerase enzymes of these ciliates synthesize telomeric repeat units distinct from that in mammals. The nucleic acids comprising the RNA of a mammalian telomerase are provided in U.S. Patent No. 5,583,016.

The functioning of telomerases seems to be activated in dividing embryonic cells and gametocytes. Telomerase activity has been identified in germ line cells and tumor

cells but is repressed in differentiated somatic cells. It is now believed that the reactivation of telomerase is an essential step in tumor progression and in the immortalization of cells in culture. It is postulated that inhibition of telomerase in an immortalized cell line or in the malignant condition would cause senescence or cell death. The introduction of synthetic oligonucleotides which mimic telomere motifs has been shown to inhibit the proliferation of immortal cells or cells that express telomerase (U.S. Patent Number 5,643,890). In fact, the single telomere motif TTAGGG exhibited greater cellular uptake and higher inhibition of proliferation than longer oligonucleotides. Methods for screening for agents which inhibit telomerase activity, including fungal telomerase activity, are provided in U.S. Patent Number 5,645,986.

Comprehensive reviews of both telomeres and telomerase are provided in U.S. Patent Numbers 5,643,890 and 5,707,795.

Telomere-Telomere Recombination

Telomere-telomere recombination provides an alternate pathway for telomere maintenance in at least some eukaryotes (Zakian, 1997). Wang *et al.* (1990) provided evidence for a telomere-telomere recombination process in yeast which involves a gene conversion event that requires little homology, occurs at or near the boundary of telomeric and non-telomeric DNA, and resembles the recombination process involved in bacteriophage T4 DNA replication.

Yeast cells which lack a functional *est1* gene exhibit a continuous decline in the terminal $(G_{1\text{-}3}\ T)_n$ tract, a progressive increase in the frequency of chromosome loss, and a concomitant increase in the frequency of cell death (Lundblad *et al.*, 1989). Although EST1 is not a catalytic component of telomerase (Cohn *et al.*, 1995), the same phenotypes are produced by deleting the *S. cerevisiae* telomerase RNA gene, *tlc1* (Singer and Gottschling, 1994). Although the majority of the cells in an $EST1^-$ culture die, late $EST1^-$ cultures give rise to derivatives that have survived the lethal consequences of the *est1* mutation. By studying the survival of late cultures of *S. cerevisiae* cells, Lundblad *et al.* (1993) demonstrated that yeast cells have a RAD52-dependent bypass pathway by which

cells can circumvent a defect in the EST1-mediated pathway for yeast telomere replication. Most of the surviving cells have very short telomeres but acquire long tandem arrays of subtelomeric repeats by gene conversion. The researchers concluded that "even when the primary pathway for telomer replication is defective, an alternative backup pathway exists that restores sufficient telomere function for continued cell viability."

Although deletion of the telomerase RNA gene, *ter1*, in the yeast *Kluyveromyces lactis* also results in the gradual loss of telomeric repeats and progressively declining cell growth capability, some cells are able to continuing growing without telomerase. McEachern et al. (1996) proposed that shortened, terminal telomeric repeat tracts become uncapped, promoting recombinational repair between them to regenerate lengthened telomeres in survivors. They termed this process telomere cap-prevented recombination (CPR).

The TERT Proteins of the Present Invention

The present invention provides isolated proteins, allelic variants of the proteins, and conservative amino acid substitutions of the proteins. As used herein, the proteins or polypeptides refers to a protein that has the amino acid sequence depicted in SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10. The invention includes naturally occurring allelic variants and proteins that have a slightly different amino acid sequence than that specifically recited for SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10. Allelic variants, though possessing a slightly different amino acid sequence than those recited above, will still have the same or similar biological functions associated with the TERT proteins specifically identified herein.

As used herein, the family of proteins related to the TERT proteins of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 refer to proteins that have been isolated from organisms in addition to *P. falciparum, C. albicans* or *O. sativa*, wherein such proteins display unique features associated with the proteins of the present invention. The methods used to identify and isolate other members of protein

families related to each of the TERT proteins of the present invention are described below.

The proteins of the present invention are preferably in isolated form. As used herein, a protein is said to be isolated when physical, mechanical or chemical methods are employed to remove the protein from cellular constituents that are normally associated with the protein. A skilled artisan can readily employ standard purification methods to obtain an isolated protein.

The proteins of the present invention further include conservative variants of the proteins herein described. As used herein, a conservative variant refers to alterations in the amino acid sequence that do not adversely affect the biological functions of the protein. A substitution, insertion or deletion is said to adversely affect the protein when the altered sequence prevents or disrupts a biological function associated with the protein. For example, the overall charge, structure or hydrophobic/hydrophilic properties of the protein can be altered without adversely affecting a biological activity. Accordingly, the amino acid sequence can be altered, for example to render the peptide more hydrophobic or hydrophilic, without adversely affecting the biological activities of the protein. Ordinarily, the allelic variants, the conservative substitution variants, and the members of the protein family will have an amino acid sequence having at least 30% amino acid sequence identity with the sequences set forth in SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10, or at least 35%, or at least 40%, or at least 45%, or at least 50%, or at least 55%, or at least 60%, or at least 65%, or at least 70%, or at least 75%, preferably at least 80%, or more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95%. Identity or homology with respect to such sequences is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the known peptides, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology, and not considering any conservative substitutions as part of the sequence identity. In a related aspect, conservative substitution refers to a substitution of one amino acid for another with generally similar properties (size, hydrophobicity, charge, etc). N-terminal,

C-terminal or internal extensions, deletions, or insertions into the peptide sequence shall not be construed as affecting homology.

Thus, the proteins of the present invention include molecules having the amino acid sequence disclosed in SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; fragments thereof having a consecutive sequence of at least about 3, 4, 5, 6, 10, 15, 20, 25, 30, 35 or more amino acid residues of the newly identified TERT proteins; amino acid sequence variants of such sequence wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed sequence; and amino acid sequence variants of the disclosed sequence, or their fragments as defined above, that have been substituted by another residue. Contemplated variants further include those containing predetermined mutations by, *e.g.*, homologous recombination, site-directed or PCR mutagenesis, and the corresponding TERT proteins of other eukaryotic species, and the alleles or other naturally occurring variants of the families of TERT proteins; and derivatives wherein the TERT proteins have been covalently modified by substitution, chemical, enzymatic, or other appropriate means with a moiety other than a naturally occurring amino acid (for example a detectable moiety such as an enzyme or radioisotope).

As described below, members of the families of TERT proteins can be used: 1) to identify agents which modulate at least one activity of the TERT proteins; 2) in methods of identifying binding partners for the TERT proteins, 3) as antigens to raise polyclonal or monoclonal antibodies, and 4) as therapeutic agents.

TERT Nucleic Acid Molecules of the Present Invention

The present invention further provides nucleic acid molecules that encode the proteins having SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 and the related proteins herein described, preferably in isolated form. As used herein, "nucleic acid" is defined as RNA or DNA that encodes a protein or peptide as defined above, or is complementary to nucleic acid sequence encoding such peptides, or hybridizes to such nucleic acids and remains stably bound to it under appropriate

stringency conditions, or encodes polypeptides sharing at least 30% sequence identity, or at least 35%, or at least 40%, or at least 45%, or at least 50%, or at least 55%, or at least 60%, or at least 65%, or at least 70%, or at least 75%, preferably at least 80%, or more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95%, with the TERT peptide sequences. Specifically contemplated are genomic DNA, cDNA, mRNA and antisense molecules, as well as nucleic acids based on alternative backbones or including alternative bases whether derived from natural sources or synthesized. Such hybridizing or complementary nucleic acids, however, are defined further as being novel and unobvious over any prior art nucleic acid including that which encodes, hybridizes under appropriate stringency conditions, or is complementary to nucleic acid encoding a protein according to the present invention.

Homology or identity is determined by **BLAST** (**B**asic **L**ocal **A**lignment **S**earch **T**ool) analysis using the algorithm employed by the programs **blastp**, **blastn**, **blastx**, **tblastn** and **tblastx** (Karlin, *et al., Proc Natl Acad Sci USA* **87**: 2264-2268, 1990 and Altschul, S. F., *J Mol Evol* **36**: 290-300, 1993, fully incorporated by reference) which are tailored for sequence similarity searching. The approach used by the **BLAST** program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases, see Altschul *et al.* (*Nature Genetics* **6**: 119-129, 1994) which is fully incorporated by reference. The search parameters for **histogram**, **descriptions**, **alignments**, **expect** (*i.e.*, the statistical significance threshold for reporting matches against database sequences), **cutoff**, **matrix** and **filter** are at the default settings. The default scoring matrix used by **blastp**, **blastx**, **tblastn**, and **tblastx** is the **BLOSUM62** matrix (Henikoff, *et al., Proc Natl Acad Sci* USA **89**: 10915-10919, 1992 fully incorporated by reference). For **blastn**, the scoring matrix is set by the ratios of **M** (*i.e.*, the reward score for a pair of matching residues) to **N** (*i.e.*, the penalty score for mismatching residues), wherein the default values for **M** and **N** are 5 and -4, respectively.

"Stringent conditions" are those hybridization conditions that work for Southern blots : hybridization with 32P nick translated probe is done in 6X SSC, 5X Denhardt's solution, 0.5% SDS, 10 mM EDTA pH8, 100 mcg/ml sheared, denatured salmon sperm DNA at 65C. Washes are at room temperature for 2X 30 min in 2X SSC, 0.1% SDS, followed by 2X30 min at 65C in 0.1X SSC, 0.1% SDS.

These conditions work, for example, for both of the *Candida* genes discovered by the present invention. For other *Candida* strains this process will still successfully work at 60C.

A skilled artisan can readily determine and vary the stringency conditions appropriately to obtain a clear and detectable hybridization signal. For example, sufficient stringency conditions are contemplated such that target (*e.g.*, SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9) and closely related sequences can be distinguished and isolated (see Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2nd ed pp. 9.47-9.58; 11.1-11.19 and 11.45-11-57, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989 and Methods in Enzymology, Vol.**152**, (Berger *et al.*, eds), pp.399-407 and 620-622, Academic Press, Inc., New York 1987).

The present invention further provides synthetic polynucleotides which may be synthesized by well-known techniques as described in the technical literature. See, *e.g.*, Carruthers *et al.*, 1982, Cold Spring Harbor Symp. Quant. Biol. 47:411-418 and Adams *et al.*, 1983, J. Am. Chem. Soc. 105:661. Double stranded DNA fragments may then be obtained either by synthesizing the complementary strand and annealing the strands together under appropriate conditions, or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

As used herein, a nucleic acid molecule is said to be "isolated" when the nucleic acid molecule is substantially separated from contaminant nucleic acid encoding other polypeptides from the source of nucleic acid.

The present invention further provides fragments of the encoding nucleic acid molecules. As used herein, a fragment of an encoding nucleic acid molecule refers to a small portion of

the entire protein encoding sequence. The size of the fragment will be determined by the intended use. For example, if the fragment is chosen so as to encode an active portion of the proteins, the fragment will need to be large enough to encode the functional region(s) of the proteins. If the fragment is to be used as a nucleic acid probe or PCR primer, then the fragment length is chosen so as to obtain a relatively small number of false positives during probing/priming.

Fragments of the encoding nucleic acid molecules of the present invention (*i.e.*, synthetic oligonucleotides) that are used as probes or specific primers for the polymerase chain reaction (PCR), or to synthesize gene sequences encoding proteins of the invention can easily be synthesized by chemical techniques, for example, the phosphotriester method of Matteucci, *et al.*, (*J. Am. Chem. Soc.* **103**:3185-3191, 1981) or using automated synthesis methods. In addition, larger DNA segments can readily be prepared by well known methods, such as synthesis of a group of oligonucleotides that define various modular segments of the gene, followed by ligation of oligonucleotides to build the complete modified gene.

The encoding nucleic acid molecules of the present invention may further be modified so as to contain a detectable label for diagnostic and probe purposes. A variety of such labels are known in the art and can readily be employed with the encoding molecules herein described. Suitable labels include, but are not limited to, biotin, radiolabeled nucleotides and the like. A skilled artisan can employ any of the art known labels to obtain a labeled encoding nucleic acid molecule.

Modifications to the primary structures themselves by deletion, addition, or alteration of the amino acids incorporated into the protein sequences during translation can be made without destroying the activity of the TERT proteins. Such substitutions or other alterations result in proteins having an amino acid sequence encoded by a nucleic acid falling within the contemplated scope of the present invention.

Isolation of Other Related Nucleic Acid Molecules

As described above, the identification of the TERT nucleic acid molecules having SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9 allows a skilled artisan

to isolate nucleic acid molecules that encode other members of the protein families of each organism in addition to the specific sequences herein described. Further, the presently disclosed nucleic acid molecules allow a skilled artisan to isolate nucleic acid molecules that encode other members of the families of proteins in addition to the amino acid protein having SEQ ID NO.2, SEQ ID NO. 4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

Essentially, a skilled artisan can readily use the amino acid sequence of SEQ ID NO.2, SEQ ID NO. 4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 to generate antibody probes to screen expression libraries prepared from appropriate cells. Typically, polyclonal antiserum from mammals such as rabbits immunized with the purified proteins (as described below) or monoclonal antibodies can be used to probe a cDNA or genomic expression library, such as lambda gtll library, to obtain the appropriate coding sequence for other members of the protein families. The cloned cDNA sequence can be expressed as a fusion protein, expressed directly using its own control sequences, or expressed by constructions using control sequences appropriate to the particular host used for expression of the enzyme.

Alternatively, a portion of the coding sequences herein described can be synthesized and used as probes to retrieve DNA encoding a member of the protein families from any eukaryotic organism. Oligomers containing approximately 18-20 nucleotides (encoding about a 6-7 amino acid stretch) are prepared and used to screen genomic DNA or cDNA libraries to obtain hybridization under stringent conditions or conditions of sufficient stringency to eliminate an undue level of false positives.

Additionally, pairs of oligonucleotide primers can be prepared for use in a polymerase chain reaction (PCR) to selectively clone an encoding nucleic acid molecule. A PCR denature/anneal/extend cycle for using such PCR primers is well known in the art and can readily be adapted for use in isolating other encoding nucleic acid molecules.

Methods to Identify Pathogen Infection, Disease Progression and Success/Failure of Treatment

U.S. Patent No. 5,489,508 sets forth general methods useful for determining the telomere

length and telomere activity of a cell based on elongating oligonucleotide primers that can serve as a substrate for telomerase-mediated primer extension under conditions which minimize interference from other genomic sequences. U.S. Patent No. 5,695,932 sets forth telomerase activity assays for diagnosing pathogenic infections, including those of *Candida* and *P. falciparum*. These methods are based on detecting the telomeric nucleic acids particular to a specific pathogen. The telomeric nucleic acids utilized by these methods are the specific telomeric repeats which a particular telomerase adds to the ends of the chromosomes. The methods set forth in these patents do not directly utilize a TERT gene or a TERT protein specific to a pathogen.

TERT expression has been suggested as a useful marker in diagnosing human gastric carcinomas and bladder cancer (Yasui *et al.*, 1998; Ito *et al.*, 1998).

Until the present invention, the TERT genes and TERT proteins of *P. falciparum* and *C. albicans* were not available for use in methods which can more directly detect these pathogens.

Thus, another embodiment of the present invention provides methods for detecting the presence or absence of a pathogen in a cell, tissue, organ or organism by analyzing the cell, tissue, organ or organism for the TERT mRNA, TERT DNA or TERT protein particular to the pathogen of interest. The present invention also provides methods for diagnosing the status of an infection in a cell, tissue, organ or organism by analyzing the cell, tissue, organ or organism for the TERT mRNA, TERT DNA or TERT protein particular to the pathogen of interest. The TERT mRNA, TERT DNA or TERT protein can be isolated or assayed by methods well known to one skilled in the art of isolating and assaying for nucleic acids and proteins. The genus or species of the organism which can be analyzed by the methods of the present invention includes, but are not limited to, any mammal.

The detection and diagnosis methods encompassed by the present invention include those using fragments, segments or portions of the specific TERT nucleic acids or TERT proteins of the present invention, where such fragments, segments or portions are indicative of the TERT mRNA, TERT DNA or TERT protein particular to the organism of interest.

Particular embodiments of the present invention include methods of detecting the presence

or absence of *C. albicans* or *P. falciparum* in a mammalian cell, tissue, organ or organism. SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO.3 or SEQ ID NO.4 can be used in methods for the detection and diagnosis of *C. albicans*. SEQ ID NO. 5, SEQ ID NO.6, SEQ ID NO.7 or SEQ ID NO.8 can be used in methods for the detection and diagnosis of *P. falciparum*.

A further embodiment of the present invention provides methods for determining the presence or absence of a pathogen by measuring the level of telomerase activity of the pathogen within a cell, tissue, organ or organism. The level of the telomerase activity can be compared to that of normal cells in that tissue, organ or organism or compared to normal cells of organisms known not to be afflicted with the pathogen.

A still further embodiment of the present invention provides methods for determining the relative or actual amount of a pathogen in a cell, tissue , organ or organism by analyzing the cell, tissue organ or organism for TERT mRNA, TERT DNA or TERT protein of the pathogen. The methods encompassed by the present invention include using fragments, segments or portions of these nucleic acids or proteins in such detection methods, where such fragments, segments or portions are indicative of the pathogen. Particular embodiments of the present invention include methods of detecting the presence or absence of *C. albicans* or *P. falciparum* in a mammalian cell, tissue, organ or organism. SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO.3 or SEQ ID NO.4 can be used in methods for determining the relative or actual amounts of *C. albicans* in a sample. SEQ ID NO. 5, SEQ ID NO.6, SEQ ID NO.7 or SEQ ID NO.8 can be used in methods for determining the relative or actual amounts of *P. falciparum* in a sample.

Methods to Identify Binding Partners

Another embodiment of the present invention provides methods for use in isolating and identifying binding partners of proteins of the invention In detail, a TERT protein or TERT protein fragment of the invention is mixed with a potential binding partner or an extract or fraction of a cell under conditions that allow the association of potential binding partners with the protein of the invention. After mixing, peptides, polypeptides, proteins or other molecules that have become associated with a proteins of the invention are

separated from the mixture. The binding partner that binds to the proteins of the invention can then be removed and further analyzed. To identify and isolate a binding partner, the entire proteins, for instance the entire amino acid protein of SEQ ID NO.2, SEQ ID NO. 4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 can be used. Alternatively, a fragment of the proteins can be used. For example, the protein fragments encoded by SEQ ID NO.8 or SEQ ID NO.10 can be utilized in the present invention.

As used herein, a cellular extract refers to a preparation or fraction which is made from a lysed or disrupted cell of the organism of interest. The preferred source of cellular extracts will be cells derived from yeast, protozoan, human or plant tissue. Cells of interest include neoplastic cells and normal cells. Alternatively, cellular extracts may be prepared from available cell lines or newly-created cell lines, particularly transformed and proliferating cells.

A variety of methods can be used to obtain an extract of a cell. Cells can be disrupted using either physical or chemical disruption methods. Examples of physical disruption methods include, but are not limited to, sonication and mechanical shearing. Examples of chemical lysis methods include, but are not limited to, detergent lysis and enzyme lysis. A skilled artisan can readily adapt methods for preparing cellular extracts in order to obtain extracts for use in the present methods.

Once an extract of a cell is prepared, the extract is mixed with the proteins of the invention under conditions in which association of the proteins with the binding partners can occur. A variety of conditions can be used, the most preferred being conditions that closely resemble conditions found in the cytoplasm of a yeast, protozoan, human or plant cell. Features such as osmolarity, pH, temperature, and the concentration of cellular extract used, can be varied to optimize the association of the proteins with the binding partners.

After mixing under appropriate conditions, the bound complex is separated from the mixture. A variety of techniques can be utilized to separate the mixture. For example, antibodies specific to a proteins of the invention can be used to immunoprecipitate the binding partner complex. Alternatively, standard chemical separation techniques such as

chromatography and density/sediment centrifugation can be used.

After removal of non-associated cellular constituents found in the extract, the binding partner can be dissociated from the complex using conventional methods. For example, dissociation can be accomplished by altering the salt concentration or pH of the mixture. To aid in separating associated binding partner pairs from the mixed extract, the proteins of the invention can be immobilized on a solid support. For example, the proteins can be attached to a nitrocellulose matrix or acrylic beads. Attachment of the proteins to a solid support aids in separating peptide/binding partner pairs from other constituents found in the extract. The identified binding partners can be either a single protein or a complex made up of two or more proteins. Alternatively, binding partners may be identified using a Far-Western assay according to the procedures of Takayama *et al., Methods Mol Biol* **69**:171-84, 1997 or Sauder *et al., J GenVirol* **77**(5):991-6, 1996 or identified through the use of epitope tagged proteins or GST fusion proteins.

Alternatively, the nucleic acid molecules of the invention can be used in a yeast two-hybrid system. The yeast two-hybrid system has been used to identify other protein partner pairs and can readily be adapted to employ the nucleic acid molecules herein described.

Methods to Identify Agents that Modulate the Expression of a Nucleic Acid Encoding the TERT Proteins of the Present Invention.

Methods of screening for agents which inhibit telomerase activity and more specifically methods of inhibiting human telomerase activity are set forth in U.S. Patent No. 5,645,986. Such methods require combining a potential agent, an active telomerase, a substrate oligonucleotide for the telomerase and nucleotide triphosphates. These methods further require using an oligonucleotide probe which hybridizes to the specific telomere repeat sequences which are added. The telomeric nucleic acid probes utilized by these methods are specific for the telomeric repeats which a particular telomerase adds to the ends of the chromosomes. U.S. Patent No. 5,830,644 sets forth methods of screening to identify an agent which increases telomerase activity in a cell by comparing the

telomerase activity of treated and untreated cells. The methods set forth in these patents do not directly utilize a TERT gene or a TERT protein of a specific pathogen.

Until the present invention, the TERT genes and TERT proteins of *P. falciparum* and *C. albicans* were not available for use in methods of screening for agents which inhibit or promote the growth of these pathogens.

Thus, another embodiment of the present invention provides methods for identifying agents that modulate the expression of a nucleic acid encoding a protein of the invention such as a protein having the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10. Such assays may utilize any available means of monitoring for changes in the expression level of the nucleic acids of the invention. As used herein, an agent is said to modulate the expression of a nucleic acid of the invention, for instance a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10, if it is capable of up- or down-regulating expression of the nucleic acid in a cell.

In one assay format, cell lines that contain reporter gene fusions between the open reading frame defined by SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9 and any assayable fusion partner may be prepared. Numerous assayable fusion partners are known and readily available including the firefly luciferase gene and the gene encoding chloramphenicol acetyltransferase (Alam *et al.* (1990) *Anal Biochem* **188**:245-254). Cell lines containing the reporter gene fusions are then exposed to the agent to be tested under appropriate conditions and time. Differential expression of the reporter gene between samples exposed to the agent and control samples identifies agents which modulate the expression of a nucleic acid encoding a protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

Additional assay formats may be used to monitor the ability of the agent to modulate the expression of a nucleic acid encoding a protein of the invention such as the protein having SEQ ID NO.2, SEQ ID NO.4, SEQ, ID NO.6, SEQ ID NO.8 or SEQ ID NO.10. For instance, mRNA expression may be monitored directly by hybridization to the nucleic acids of the invention. Cell lines are exposed to the agent to be tested under appropriate

conditions and time and total RNA or mRNA is isolated by standard procedures such those disclosed in Sambrook *et al.* (Molecular Cloning: A Laboratory Manual, 2nd Ed. Cold Spring Harbor Laboratory Press, 1989).

In order to assay gene expression of the present invention in a physiologically relevant manner, tissues may be analyzed under conditions which model neoplastic or normal cell stages of proliferation and differentiation. Cells which express or fail to express a particular gene involved in the activation, inactivation or regulation of TERT transcription and expression may be particularly useful in the assays discussed herein. Such cells can exist naturally or be the result of genetic manipulation, such as specialized cells created via gene transformation or gene disruption. For example, cells with or without the MYC proto-oncogene may be of interest in methods used for identifying agents which modulate TERT gene expression. The MYC proto-oncogene encodes a ubiquitous transcription factor (c-MYC) involved in the control of cell proliferation and differentiation (Wu *et al.*, 1999). TERT and c-MYC are expressed in normal and transformed proliferating cells, downregulated in quiescent and terminally differentiated cells, and can both induce immortalization when constitutively expressed in transfected cells. As another example, telomerase activity is suppressed during terminal differentiation of HL-60 promyelocytic leukaemic cells (Xu *et al.*, 1999).

Probes to detect differences in RNA expression levels between cells exposed to the agent and control cells may be prepared from the nucleic acids of the invention. It is preferable, but not necessary, to design probes which hybridize only with target nucleic acids under conditions of high stringency. Only highly complementary nucleic acid hybrids form under conditions of high stringency. Accordingly, the stringency of the assay conditions determines the amount of complementarity which should exist between two nucleic acid strands in order to form a hybrid. Stringency should be chosen to maximize the difference in stability between the probe:target hybrid and potential probe:non-target hybrids.

Probes may be designed from the nucleic acids of the invention through methods known in the art. For instance, the G+C content of the probe and the probe length can

affect probe binding to its target sequence. Methods to optimize probe specificity are commonly available in Sambrook *et al.* (Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, NY, 1989) or Ausubel *et al.* (Current Protocols in Molecular Biology, Greene Publishing Co., NY, 1995).

Hybridization conditions are modified using known methods, such as those described by Sambrook *et al.* and Ausubel *et al.* as required for each probe. Hybridization of total cellular RNA or RNA enriched for polyA RNA can be accomplished in any available format. For instance, total cellular RNA or RNA enriched for polyA RNA can be affixed to a solid support and the solid support exposed to at least one probe comprising at least one, or part of one of the sequences of the invention under conditions in which the probe will specifically hybridize. Alternatively, nucleic acid fragments comprising at least one, or part of one of the sequences of the invention can be affixed to a solid support, such as a porous glass wafer. The glass wafer can then be exposed to total cellular RNA or polyA RNA from a sample under conditions in which the affixed sequences will specifically hybridize. Such glass wafers and hybridization methods are widely available, for example, those disclosed by Beattie (WO 95/11755). By examining for the ability of a given probe to specifically hybridize to an RNA sample from an untreated cell population and from a cell population exposed to the agent, agents which up or down regulate the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 are identified.

Hybridization for qualitative and quantitative analysis of mRNAs may also be carried out by using a RNase Protection Assay (*i.e.*, RPA, see Ma *et al.*, *Methods* **10**: 273-238, 1996). Briefly, an expression vehicle comprising cDNA encoding the gene product and a phage specific DNA dependent RNA polymerase promoter (e.g., T7, T3 or SP6 RNA polymerase) is linearized at the 3' end of the cDNA molecule, downstream from the phage promoter, wherein such a linearized molecule is subsequently used as a template for synthesis of a labeled antisense transcript of the cDNA by *in vitro* transcription. The labeled transcript is then hybridized to a mixture of isolated RNA (*i.e.*, total or fractionated mRNA) by incubation at 45°C overnight in a buffer comprising 80%

formamide, 40 mM Pipes, pH 6.4, 0.4 M NaCl and 1 mM EDTA. The resulting hybrids are then digested in a buffer comprising 40 μg/ml ribonuclease A and 2 μg/ml ribonuclease. After deactivation and extraction of extraneous proteins, the samples are loaded onto urea/polyacrylamide gels for analysis.

In another assay format, agents which effect the expression of the instant gene products, cells or cell lines would first be identified which express said gene products physiologically. Cell and/or cell lines so identified would be expected to comprise the necessary cellular machinery such that the fidelity of modulation of the transcriptional apparatus is maintained with regard to exogenous contact of agent with appropriate surface transduction mechanisms and/or the cytosolic cascades. Further, such cells or cell lines would be transduced or transfected with an expression vehicle (*e.g.*, a plasmid or viral vector) construct comprising an operable non-translated 5'-promoter containing end of the structural gene encoding the instant gene products fused to one or more antigenic fragments, which are peculiar to the instant gene products, wherein said fragments are under the transcriptional control of said promoter and are expressed as polypeptides whose molecular weight can be distinguished from the naturally occurring polypeptides or may further comprise an immunologically distinct tag. Such a process is well known in the art (see Maniatis, 1982). Elements responsible for promoter activity of hTERT are known to be contained within a region extending from 330 bp upstream of the ATG to the second exon of the hTERT gene (Cong *et al.*, 1999).

Cells or cell lines transduced or transfected as outlined above would then be contacted with agents under appropriate conditions; for example, the agent comprises a pharmaceutically acceptable excipient and is contacted with cells comprised in an aqueous physiological buffer such as phosphate buffered saline (PBS) at physiological pH, Eagles balanced salt solution (BSS) at physiological pH, PBS or BSS comprising serum or conditioned media comprising PBS or BSS and/or serum incubated at 37° C. Said conditions may be modulated as deemed necessary by one of skill in the art. Subsequent to contacting the cells with the agent, said cells will be disrupted and the polypeptides of the disruptate are fractionated such that a polypeptide fraction is pooled

and contacted with an antibody to be further processed by immunological assay (*e.g.*, ELISA, immunoprecipitation or Western blot). The pool of proteins isolated from the "agent contacted" sample will be compared with a control sample where only the excipient is contacted with the cells and an increase or decrease in the immunologically generated signal from the "agent contacted" sample compared to the control will be used to distinguish the effectiveness of the agent.

Methods to Identify Agents that Modulate at Least One Activity of the TERT Proteins.

Another embodiment of the present invention provides methods for identifying agents that modulate at least one activity of a protein of the invention such as the protein having the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10. Such methods or assays may utilize any means of monitoring or detecting the desired activity, such as the synthesis of telomeric DNA, cell immortalization, tumorigenesis or cell proliferation.

In one format, an assay may involve comparing the relative amounts of a protein of the present invention between a cell population that has been exposed to the agent to be tested to that of an un-exposed control cell population. In this format, probes such as specific antibodies are used to monitor the differential expression of the protein in the different cell populations. Cell lines or populations are exposed to the agent to be tested under appropriate conditions and time. Cellular lysates may be prepared from the exposed cell line or population and a control, unexposed cell line or population. The cellular lysates are then analyzed with the probe.

Antibody probes are prepared by immunizing suitable mammalian hosts in appropriate immunization protocols using the peptides, polypeptides or proteins of the invention if they are of sufficient length, or, if desired, or if required to enhance immunogenicity, conjugated to suitable carriers. Methods for preparing immunogenic conjugates with carriers such as BSA, KLH, or other carrier proteins are well known in the art. In some circumstances, direct conjugation using, for example, carbodiimide

reagents may be effective; in other instances linking reagents such as those supplied by Pierce Chemical Co., Rockford, IL, may be desirable to provide accessibility to the hapten. The hapten peptides can be extended at either the amino or carboxy terminus with a Cys residue or interspersed with cysteine residues, for example, to facilitate linking to a carrier. Administration of the immunogens is conducted generally by injection over a suitable time period and with use of suitable adjuvants, as is generally understood in the art. During the immunization schedule, titers of antibodies are taken to determine adequacy of antibody formation.

While the polyclonal antisera produced in this way may be satisfactory for some applications, for pharmaceutical compositions, use of monoclonal preparations is preferred. Immortalized cell lines which secrete the desired monoclonal antibodies may be prepared using the standard method of Kohler and Milstein (*Nature* **256**(5517):495-7, 1975; *Eur J Immunol* **6**(7):511-9, 1976; and *Biotechnology* **24**:524-6, 1992)or modifications which effect immortalization of lymphocytes or spleen cells, as is generally known. The immortalized cell lines secreting the desired antibodies are screened by immunoassay in which the antigen is the peptide hapten. polypeptide or protein. When the appropriate immortalized cell culture secreting the desired antibody is identified, the cells can be cultured either *in vitro* or by production in ascites fluid.

The desired monoclonal antibodies are then recovered from the culture supernatant or from the ascites supernatant. Fragments of the monoclonals or the polyclonal antisera which contain the immunologically significant portion can be used as antagonists, as well as the intact antibodies. Use of immunologically reactive fragments, such as the Fab, Fab', of $F(ab')_2$ fragments is often preferable, especially in a therapeutic context, as these fragments are generally less immunogenic than the whole immunoglobulin.

The antibodies or fragments may also be produced, using current technology, by recombinant means. Antibody regions that bind specifically to the desired regions of the protein can also be produced in the context of chimeras with multiple species origin, for instance, humanized antibodies.

Agents that are assayed in the above method can be randomly selected or rationally

selected or designed. As used herein, an agent is said to be randomly selected when the agent is chosen randomly without considering the specific sequences involved in the association of the a protein of the invention alone or with its associated substrates, binding partners, etc. An example of randomly selected agents is the use a chemical library or a peptide combinatorial library, or a growth broth of an organism.

As used herein, an agent is said to be rationally selected or designed when the agent is chosen on a nonrandom basis which takes into account the sequence of the target site and/or its conformation in connection with the agent's action. Agents can be rationally selected or rationally designed by utilizing the peptide sequences that make up these sites.

The agents of the present invention can be, as examples, peptides, small molecules, vitamin derivatives, as well as carbohydrates. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of the present invention.

The peptide agents of the invention can be prepared using standard solid phase (or solution phase) peptide synthesis methods, as is known in the art. In addition, the DNA encoding these peptides may be synthesized using commercially available oligonucleotide synthesis instrumentation and produced recombinantly using standard recombinant production systems. The production using solid phase peptide synthesis is necessitated if non-gene-encoded amino acids are to be included.

Another class of agents of the present invention are antibodies immunoreactive with critical positions of proteins of the invention. Antibody agents are obtained by immunization of suitable mammalian subjects with peptides, containing as antigenic regions, those portions of the protein intended to be targeted by the antibodies.

Uses for Agents that Modulate at Least One Activity of the TERT Proteins.

Agents that modulate or down-regulate the expression of the protein or agents such as agonists or antagonists of at least one activity of the proteins may be used to modulate biological and pathologic processes associated with the protein's function and activity. As used herein, a subject can be any mammal, so long as the mammal is in need of modulation of a pathological or biological process mediated by a protein of the invention.

The term "mammal" is meant to include an individual belonging to the class Mammalia. The invention is particularly useful in the treatment of human subjects with conditions or diseases such as cancer, such as stomach cancer, malaria or vaginal candidiasis.

Pathological processes refer to a category of biological processes which produce a deleterious effect. For example, expression of a protein of the invention may be associated with tumorigenesis, malaria or vaginal candidiasis. The pathological processes associated with malaria and a list of drugs currently used in the chemotherapy of protozoal infections are set forth in J.W. Tracy and L.T. Webster, Jr., 1996, Malaria, In Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, Ch. 40:965-985.

As used herein, an agent is said to modulate a pathological process when the agent reduces the degree or severity of the process. For instance, malaria may be prevented or disease progression modulated by the administration of agents which reduce or modulate in some way the expression or at least one activity of a protein, a gene, or a gene product (RNA or DNA) of the invention.

The agents of the present invention can be provided alone, or in combination with other agents that modulate a particular pathological process. For example, an agent of the present invention can be administered in combination with other agents commonly used to treat cancers, protozoan infections and yeast infections. As used herein, two agents are said to be administered in combination when the two agents are administered simultaneously or are administered independently in a fashion such that the agents will act at the same time.

The agents of the present invention can be administered via parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The present invention further provides compositions containing one or more agents which modulate expression or at least one activity of a protein of the invention. While

individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typical dosages comprise 0.1 to 100 μg/kg body wt. The preferred dosages comprise 0.1 to 10 μg/kg body wt. The most preferred dosages comprise 0.1 to 1 μg/kg body wt.

In addition to the pharmacologically active agent, the compositions of the present invention may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically for delivery to the site of action. Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers. Liposomes can also be used to encapsulate the agent for delivery into the cell.

The pharmaceutical formulation for systemic administration according to the invention may be formulated for enteral, parenteral or topical administration. Indeed, all three types of formulations may be used simultaneously to achieve systemic administration of the active ingredient.

Suitable formulations for oral administration include hard or soft gelatin capsules, pills, tablets, including coated tablets, elixirs, suspensions, syrups or inhalations and controlled release forms thereof.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents,

thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

rDNA molecules Containing a Nucleic Acid Molecule

The present invention further provides recombinant DNA molecules (rDNAs) that contain coding sequences. As used herein, a rDNA molecule is a DNA molecule that has been subjected to molecular manipulation *in situ*. Methods for generating rDNA molecules are well known in the art, for example, see Sambrook *et al., Molecular Cloning* (1989). In the preferred rDNA molecules, a coding DNA sequence is operably linked to expression control sequences and/or vector sequences.

The choice of vector and/or expression control sequences to which one of the protein family encoding sequences of the present invention is operably linked depends directly, as is well known in the art, on the functional properties desired, *e.g.*, protein expression, and the host cell to be transformed. A vector contemplated by the present invention is at least capable of directing the replication or insertion into the host chromosome, and preferably also expression, of the structural gene included in the rDNA molecule.

Expression control elements that are used for regulating the expression of an operably linked proteins encoding sequence are known in the art and include, but are not limited to, inducible promoters, constitutive promoters, secretion signals, and other regulatory elements. Preferably, the inducible promoter is readily controlled, such as being responsive to a nutrient in the host cell's medium.

In one embodiment, the vector containing a coding nucleic acid molecule will include a prokaryotic replicon, *i.e.*, a DNA sequence having the ability to direct autonomous replication and maintenance of the recombinant DNA molecule extrachromosomally in a prokaryotic host cell, such as a bacterial host cell, transformed therewith. Such replicons are well known in the art. In addition, vectors that include a prokaryotic replicon may also include a gene

whose expression confers a detectable marker such as a drug resistance. Typical bacterial drug resistance genes are those that confer resistance to ampicillin or tetracycline.

Vectors that include a prokaryotic replicon can further include a prokaryotic or bacteriophage promoter capable of directing the expression (transcription and translation) of the coding gene sequences in a bacterial host cell, such as *E. coli*. A promoter is an expression control element formed by a DNA sequence that permits binding of RNA polymerase and transcription to occur. Promoter sequences compatible with bacterial hosts are typically provided in plasmid vectors containing convenient restriction sites for insertion of a DNA segment of the present invention. Typical of such vector plasmids are pUC8, pUC9, pBR322 and pBR329 available from Biorad Laboratories, (Richmond, CA), pPL and pKK223 available from Pharmacia, Piscataway, N.J.

Expression vectors compatible with eukaryotic cells can also be used to form a rDNA molecules that contains a coding sequence. Eukaryotic cell expression vectors are well known in the art and are available from several commercial sources. Typically, such vectors are provided containing convenient restriction sites for insertion of the desired DNA segment. Typical of such vectors are pSVL and pKSV-10 (Pharmacia), pBPV-1/pML2d (International Biotechnologies, Inc.), pTDT1 (ATCC, #31255), the vector pCDM8 described herein, and the like eukaryotic expression vectors.

Eukaryotic cell expression vectors used to construct the rDNA molecules of the present invention may further include a selectable marker that is effective in an eukaryotic cell, preferably a drug resistance selection marker. A preferred drug resistance marker is the gene whose expression results in neomycin resistance, i.e., the neomycin phosphotransferase (*neo*) gene. (Southern *et al.*, *J. Mol. Anal.Genet* 1:327-341, 1982.) Alternatively, the selectable marker can be present on a separate plasmid, and the two vectors are introduced by co-transfection of the host cell, and selected by culturing in the appropriate drug for the selectable marker.

Host Cells Containing an Exogenously Supplied Coding Nucleic Acid Molecule

The present invention further provides host cells transformed with nucleic acid molecules

that encode the TERT proteins of the present invention. Eukaryotic cells useful for expression of a protein of the invention are not limited, so long as the cell line is compatible with cell culture methods and compatible with the propagation of the expression vector and expression of the gene product. Preferred eukaryotic host cells include, but are not limited to, yeast, protozoan, insect, plant and mammalian cells. Preferable vertebrate cells include those from a mouse, rat, monkey or human cell line. Preferred eukaryotic host cells include Chinese hamster ovary (CHO) cells available from the ATCC as CCL61, NIH Swiss mouse embryo cells NIH/3T3 available from the ATCC as CRL 1658, HL-60 promyelocytic cells, baby hamster kidney cells (BHK), and the like eukaryotic tissue culture cell lines. Various plant cells are also preferred hosts, including those of tomato, rice, wheat, corn, tobacco, Arabidopsis, soybean and alfalfa.

Any prokaryotic host can be used to express a rDNA molecule encoding a protein of the invention. The preferred prokaryotic host is *E. coli*.

Transformation of appropriate cell hosts with a rDNA molecule of the present invention is accomplished by well known methods that typically depend on the type of vector used and host system employed. With regard to transformation of prokaryotic host cells, electroporation and salt treatment methods are typically employed, see, for example, Cohen *et al.*, *Proc. Natl. Acad. Sci. USA* **69**:2110, 1972; and Maniatis *et al.*, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1982). With regard to transformation of vertebrate cells with vectors containing rDNAs, electroporation, cationic lipid or salt treatment methods are typically employed, see, for example, Graham *et al.*, *Virol* **52**:456, 1973; Wigler *et al.*, *Proc Natl Acad Sci USA* **76**:1373-76, 1979.

Successfully transformed cells, *i.e.*, cells that contain a rDNA molecule of the present invention, can be identified by well known techniques including the selection for a selectable marker. For example, cells resulting from the introduction of an rDNA of the present invention can be cloned to produce single colonies. Cells from those colonies can be harvested, lysed and their DNA content examined for the presence of the rDNA using a method such as that described by Southern, *J Mol Biol* **98**:503, 1975, or Berent *et al.*, *Biotech.* **3**:208, 1985 or the proteins produced from the cell assayed via an immunological method.

Production of Recombinant Proteins using a rDNA Molecule

The present invention further provides methods for producing a TERT protein of the invention using nucleic acid molecules herein described. In general terms, the production of a recombinant form of a protein typically involves the following steps:

First, a nucleic acid molecule is obtained that encodes a protein of the invention, such as the nucleic acid molecules depicted in SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9, or fragments of such sequences which encode an active TERT protein. If the encoding sequences are uninterrupted by introns, it is directly suitable for expression in any host.

The nucleic acid molecules are then preferably placed in operable linkage with suitable control sequences, as described above, to form an expression units containing the open reading frame of the TERT proteins or protein fragments. The expression unit is used to transform a suitable host and the transformed host is cultured under conditions that allow the production of the recombinant proteins. Optionally the recombinant proteins are isolated from the medium or from the cells; recovery and purification of the proteins may not be necessary in some instances where some impurities may be tolerated.

Each of the foregoing steps can be done in a variety of ways. For example, the desired coding sequences may be obtained from genomic fragments and used directly in appropriate hosts. The construction of expression vectors that are operable in a variety of hosts is accomplished using appropriate replicons and control sequences, as set forth herein. The control sequences, expression vectors, and transformation methods are dependent on the type of host cell used to express the gene and were discussed in detail herein. Suitable restriction sites can, if not normally available, be added to the ends of the coding sequence so as to provide an excisable gene to insert into these vectors. A skilled artisan can readily adapt any host/expression system known in the art for use with the nucleic acid molecules of the invention to produce recombinant proteins.

Genetic Transformation Methods

Production of Transgenic Protozoans

Transgenic protozoans, especially *P. falciparum*, clones containing recombinant genes corresponding to the DNA sequences of SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9 are a part of the invention.

Protozoans expressing heterologous genes can be produced by homologous recombination of circular plasmids into the corresponding chromosome loci. For a general discussion of the molecular biology of parasitic protozoans, *see*, D.F. Smith and M. Parsons, 1996, *Molecular Biology of Parasitic Protozoa* (Frontiers in Molecular Biology, 13).

Organisms such as *P. falciparum* (Yuda *et al.*, 1999, *J. Exp. Med.*, **189(12)**:1947-1952; Menard *et al.*,1997, *Methods*, **13(2)**:148-157), *P. berghei* (van Dijk *et al.*, 1995, *Science*, **268(5215)**:1358-1362) and *Toxoplasma gondii* (Black et al., 1998, *J. Biol. Chem.*, 273(7):3972-9) have been used.

Unlike yeast and bacterial recombinant systems, the purpose of which may be commercial production of heterologous proteins, these transformants usually are produced to provide a basis for studying the effects of gene alterations and knock-outs, as well as for studying the different stages in an organism's life cycle (Wu et al., 1996, PNAS, 93(3):1130-1134; Waters *et al.*, 1997, *Methods*, 13(2):134-147).

Production of Transgenic Yeast

Transgenic yeast, especially *C. albicans*, clones containing recombinant genes corresponding to the DNA sequences of SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9 are a part of the invention.

For general discussion on producing transgenic yeasts, *see*, P.L. Bartel and S. Fields, 1997, *The Yeast Two-Hybrid System (Advances in Molecular Biology)*, Oxford Univ. Press.; A.J.P. Brown *et al.*, 1998, *Yeast Gene Analysis*; A. Adams *et al.*, 1997, *Methods in Yeast Genetics, 1997*: A Cold Spring Harbor Laboratory Course Manual/With 1999 Biosupplynet Source Book; H. Heslot and C. Gaillardin, 1991, *Molecular Biology and Genetic Engineering of Yeasts*.

The production of recombinant yeasts and their use in the subsequent production of secreted and non-secreted heterologous proteins are well known and well characterized in the art (Russo et al., 1995, *J. Environ. Pathol. Toxicol. Oncol* 14(3-4):133-157; Buckholz *et al.*, 1991, *Biotechnology*, 9(11):1067-1072; Tekamp-Olson *et al.*, 1990, *Curr. Opinion Biotechnol.* 1:28-35; Brake *et al.*, 1984, *PNAS* 81:4642-4646; Bitter *et al.*, 1984, PNAS 81:5330-5334; Singh *et al.*, 1984, Nucl. Acid. Res. 12:8927.

C. albicans can be transformed by traditional (biochemical) means (Datta *et al.*, 1989, *Adv. Microb. Physiol.* 30:53-88 and U.S. Patent Nos. 5,871,987 and 5,885,815) or by electroporation (U.S. Patent No. 5,908,753).

In addition to *C. albicans and S. cerevisiae*, other transgenic yeasts can be created by transforming, with suitable vectors and promoters, organisms such as: *Pichia pastoris* (U.S. Patent No. 4,879,231); *Kluyveromyces lactis* (U.S. Patent Nos. 4,806,472 and 5,633,146); *Hansenula polymorpha* (U.S. Patent Nos. 5,240,838 and 5,741,674); *Schizosaccharomyces pombe* (U.S. Patent No. 5,663,061), *Schwanniomyces occidentalis* (U.S. Patent No. 5,100,794) and *Yarrowia lipolytica* (U.S. Patent No. 4,880,741).

Recombinant proteins which have been successfully produced by yeast systems include, but are not limited to, alpha-interferon (U.S. Patent No. 4,615,974); human growth hormone and human insulin (U.S. Patent No. 4,775,622); platelet derived growth factor (U.S. Patent No. 4,801,542); a herpes simplex virus gene (U.S. Patent No. 5,059,538); epidermal growth factor (U.S. Patent 5,102,789); desulphatohirudin, a protease inhibitor (U.S. Patent No. 5,726,043); alpha, beta and gamma-globin (U.S. Patent No. 5,827,693); and human serum albumin (U.S. Patent No. 5,879,907).

Production of Transgenic Animals

Transgenic animals containing mutant, knock-out or modified genes corresponding to the DNA sequence of SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9 are also included in the invention.

Transgenic animals are genetically modified animals into which recombinant, exogenous or cloned genetic material has been experimentally transferred. Such genetic material is often

referred to as a transgene. The nucleic acid sequence of the transgene, in this case an active form, fragment or segment of SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9, may be integrated either at a locus of a genome where that particular nucleic acid sequence is not otherwise normally found or at the normal locus for the transgene. The transgene may consist of nucleic acid sequences derived from the genome of the same species or of a different species, including non-animal species, than the species of the target animal.

The term "germ cell line transgenic animal" refers to a transgenic animal in which the genetic alteration or genetic information was introduced into a germ line cell, thereby conferring the ability of the transgenic animal to transfer the genetic information to offspring. If such offspring in fact possess some or all of that alteration or genetic information, then they too are transgenic animals.

The alteration or genetic information may be foreign to the species of animal to which the recipient belongs, foreign only to the particular individual recipient, or may be genetic information already possessed by the recipient. In the last case, the altered or introduced gene may be expressed differently than the native gene.

The development of transgenic technology allows investigators to create mammals of virtually any genotype and to assess the consequences of introducing specific exogenous nucleic acid sequences on the physiological and morphological characteristics of the transformed animals. The availability of transgenic animals permits cellular processes to be influenced and examined in a systematic and specific manner not achievable with most other test systems. For example, the development of transgenic animals provides biological and medical scientists with models that are useful in the study of disease. Such animals are also useful for the testing and development of new pharmaceutically active substances. Gene therapy can be used to ameliorate or cure the symptoms of genetically-based diseases.

Transgenic animals can be produced by a variety of different methods including transfection, electroporation, microinjection, biolistics (also called gene particle acceleration or microprojectile bombardment), gene targeting in embryonic stem cells and recombinant viral and retro viral infection (*see, e.g.*, U.S. Patent No. 4,736,866; U.S. Patent No. 5,602,307; Mullins et al., *Hypertension* 22(4):630-633 (1993); Brenin et al., *Surg. Oncol.* 6(2)99-110

(1997); Tuan (ed.), *Recombinant Gene Expression Protocols*, Methods in Molecular Biology No. 62, Humana Press (1997)).

The term "knock-out" generally refers to mutant organisms which contain a null allele of a specific gene. The term "knock-in" generally refers to mutant organisms into which a gene has been inserted through homologous recombination. The knock-in gene may be a mutant form of a gene which replaces the endogenous, wild-type gene.

A number of recombinant rodents have been produced, including those which express an activated oncogene sequence (U.S. Patent No. 4,736,866); express simian SV 40 T-antigen (U.S. Patent No. 5,728,915); lack the expression of interferon regulatory factor 1 (IRF-1) (U.S. Patent No. 5,731,490); exhibit dopaminergic dysfunction (U.S. Patent No. 5,723,719); express at least one human gene which participates in blood pressure control (U.S. Patent No. 5,731,489); display greater similarity to the conditions existing in naturally occurring Alzheimer's disease (U.S. Patent No. 5,720,936); have a reduced capacity to mediate cellular adhesion (U.S. Patent No. 5,602,307); possess an bovine growth hormone gene (Clutter et al., *Genetics* 143(4):1753-1760 (1996)); and are capable of generating a fully human antibody response (McCarthy, *The Lancet* 349(9049):405 (1997)).

While rodents, especially mice and rats, remain the animals of choice for most transgenic experimentation, in some instances it is preferable or even necessary to use alternative animal species. Transgenic procedures have been successfully utilized in a variety of non-murine animals, including sheep, goats, pigs, dogs, cats, monkeys, chimpanzees, hamsters, rabbits, cows and guinea pigs (*see, e.g.,* Kim et al., *Mol. Reprod. Dev.* 46(4(:515-526 (1997); Houdebine, *Reprod. Nutr. Dev.* 35(6):609-617 (1995); Petters, *Reprod. Fertil. Dev.* 6(5):643-645 (1994); Schnieke et al., *Science* 278(5346):2130-2133 (1997); and Amoah, *J. Animal Science* 75(2):578-585 (1997)).

The method of introduction of nucleic acid fragments into recombination competent mammalian cells can be by any method which favors co-transformation of multiple nucleic acid molecules. Detailed procedures for producing transgenic animals are readily available to one skilled in the art, including the recitations in U.S. Patent No. 5,489,743 and U.S. Patent No. 5,602,307.

Production of Transgenic Plants

Transgenic plants can be produced by a variety of different transformation methods including, but not limited to, electroporation; microinjection; microprojectile bombardment, also known as particle acceleration or biolistic bombardment; viral-mediated transformation; and Agrobacterium-mediated transformation (*see, e.g.*, U.S. Patent Numbers 5,405,765, 5,472,869, 5,538,877, 5,538,880, 5,550,318, 5,641,664, 5,736,369 and 5,736369; Watson *et al.*, *Recombinant DNA*, Scientific American Books (1992); Hinchee et al., *Bio/Tech.* 6:915-922 (1988); McCabe et al., *Bio/Tech.* 6:923-926 (1988); Toriyama et al., *Bio/Tech.* 6:1072-1074 (1988); Fromm et al., *Bio/Tech.* 8:833-839 (1990); Mullins et al., *Bio/Tech.* 8:833-839 (1990); and Raineri et al., *Bio/Tech.* 8:33-38 (1990)).

Methods of producing transgenic rice plants are well known to those skilled in the art of plant transformation. See, *e.g.*, Hiei *et al.*, 1994, *Plant J.* 6:271-282; Christou *et al.*, 1992, *Trends in Biotechnology* 10:239; Lee *et al.*, *Proc. Nat'l Acad. Sci. USA* 88:6389, U.S. Patent Nos. 5,859,326, 5,861,542, 5,952,485, and 5,952,553.

Genes successfully introduced into plants using recombinant DNA methodologies include, but are not limited to, those coding for the following traits: seed storage proteins, including modified 7S legume seed storage proteins (U.S. Patent Numbers 5,508,468, 5,559,223 and 5,576,203); herbicide tolerance or resistance (U.S. Patent Numbers 5,498,544 and 5,554,798; Powell et al., *Science* 232:738-743 (1986); Kaniewski et al., *Bio/Tech.* 8:750-754 (1990); Day et al., *Proc. Natl. Acad. Sci. USA* 88:6721-6725 (1991)); phytase (U.S. Patent Number 5,593,963); resistance to bacterial, fungal, nematode and insect pests, including resistance to the lepidoptera insects conferred by the Bt gene (U.S. Patent Numbers 5,597,945 and 5,597,946; Hilder et al., *Nature* 330:160-163; Johnson et al., *Proc. Natl. Acad. Sci.* USA, 86:9871-9875 (1989); Perlak et al., *Bio/Tech.* 8:939-943 (1990)); lectins (U.S. Patent Number 5,276,269); and flower color (Meyer et al., *Nature* 330:677-678 (1987); Napoli et al., *Plant Cell* 2:279-289 (1990); van der Krol et al., *Plant Cell* 2:291-299 (1990)).

Homologous Recombination

Genes can be introduced in a site directed fashion using homologous recombination. This

can be used in the creation of a transgenic animal, wherein the animal would be mutated, and the phenotype of the mutation could be studied for purposes of drug screening, investigating physiologic processes, developing new products and the like. Papers discussing homologous recombination are discussed in U.S. Patent No. 5,413,923.

Homologous recombination permits site-specific modifications in endogenous genes and thus inherited or acquired mutations may be corrected, and/or novel alterations may be engineered into the genome. The application of homologous recombination to gene therapy depends on the ability to carry out homologous recombination or gene targeting in normal, somatic cells for transplantation.

To prepare cells for homologous recombination, embryonic stem cells or a stem cell line may be obtained. Cells other than embryonic stem cells can be utilized (*e.g.* hematopoietic stem cells etc.) (See U.S. Patent No. 5,589,369 for more examples). The cells may be grown on an appropriate fibroblast fetal layer or grown in the presence of leukemia inhibiting factor (LIF) and then used. The embryonic stem cells may be injected into a blastocyst, that has been previously obtained, to provide a chimeric animal. The main advantage of the embryonic stem cell technique is that the cells transfected with the "transgene" can be tested prior to reimplantation into a female animal for gestation for integration and the effect of the transgenes. By subsequent cross-breeding experiments, animals can be bred which carry the transgene on both chromosomes. If mutations are incorporated into the transgenes which block expression of the normal gene production, the endogenous genes can be eliminated by this technique and functional studies can thus be performed.

Methods for intracellularly producing DNA segments by homologous recombination of smaller overlapping DNA fragments and transgenic mammalian cells and whole animals produced by such methods are disclosed in U.S. Patent No. 5,612,205. Cell lines useful for analysis of human homologous interchromosomal recombination are provided in U.S. Patent Application No. 5,554,529.

Homologous recombination can also proceed extrachromasomally, which may be of benefit when handling large gene sequences (*e.g.*, larger than 50 kb). Methods of performing extrachromosomal homologous recombination are described in U.S. Patent No. 5,721,367.

Homologous recombination and site-directed integration in plants are discussed in U.S. Patent Nos. 5,451,513, 5,501,967 and 5,527,695.

Artificial Chromosomes

Components of Artificial Chromosomes

Artificial chromosomes are man-made linear DNA molecules constructed from essential DNA sequence elements that are responsible for the proper replication and partitioning of natural chromosomes (Murray *et al.*, 1983). The essential elements necessary to construct artificial chromosomes include:

1) a centromere, which is the site of kinetochore assembly and is responsible for the proper distribution of replicated chromosomes at cell division (*i.e.*, mitosis and meiosis);

2) two telomeres, the structures at the ends of a chromosome, which are needed to prevent the chromosome from being nibbled away by exonucleases;

3) an origin of replication, also known as Autonomous Replication Sequences (ARS), which are the positions along the chromosome at which DNA replication initiates.

The construction of functional artificial chromosomes provides an alternate method for transforming cells. Artificial chromosome vectors can be constructed to include gene sequences capable of producing specific polypeptides, wherein the gene sequences can include extremely long stretches of exogenous DNA. Of course, selectable marker genes can also be included in such artificial chromosomes to aid in the selection of transformed cells.

Use of artificial chromosome recombinant molecules as vectors solves many of the problems associated with alternative transformation technologies which are used to introduce new DNA into higher eukaryotic cells. Since artificial chromosomes are maintained in the cell nucleus as independently replicating DNA molecules, sequences introduced on such vectors are not subject to the variable expression due to integration position effects. In addition, the delivery of artificial chromosomes to the nucleus of a cell as intact, unbroken, double-stranded DNA molecules with telomeric ends ensures that the introduced DNA can be maintained stably in that form and that rearrangements should not occur. Furthermore, artificial chromosome vectors will be stably maintained in the nucleus through meiosis and

will be available to participate in homology-dependent meiotic recombination. Exogenous DNA introduced via artificial chromosome vectors can be delivered to practically any cell without host range limitations, in contrast to some other transformation methods such as the Agrobacterium-mediated DNA transfer systems.

Yeast Artificial Chromosomes

Yeast artificial chromosomes (YACs) are genetically engineered chromosomes that contain the essential DNA sequence elements of *Saccharomyces* and segments of exogenous DNAs that are much larger than those accepted by conventional cloning vectors.

YACs are generated from synthetic minichromosomes that contain a yeast centromere, a replication origin, and fused telomeres. The circular chromosome also contains three marker genes (*m1, m2, and m3*), which when expressed, allow selection of the cells carrying the plasmid and two specific sites (Burke et al, 1987). These two sites allow specific restriction endonucleases to break the molecule. Cleavage at one site opens the ring, while cleavage at the second site generates centric and acentric fragments with ends that will accept exogenous DNA fragments. Once these ends are ligated, an artificial chromosome is generated with a short and a long arm, with the long arm containing the spliced segment of exogenous DNA to be cloned. Such artificial chromosomes are distributed normally during subsequent yeast divisions creating colonies containing the YACs. In cells possessing the insert, the *m1* and *m3* markers are expressed, but the damaged M2 is not, allowing religated YACs to be distinguished from unbroken plasmids. For further descriptions of this process, see T. A. Brown, Gene Cloning, Second Edition, Chapman & Hall (1990), U.S. Patent Number 4,889,806 and U.S. Patent Number 5,270,201.

Telomeric fragments of human DNA, including the sequence for the human telomere, ranging in size from 50 to 250 kilobases have been cloned into *Saccharomyces cerevisiae* using YAC vectors (*see, e.g.*, Riethman *et al.*, 1989; Guerrini *et al.*, 1990).

YAC vectors can be constructed according to the methods detailed in U.S. Patent Nos. 4,889,806 and 5,270,201.

Yeast ARSs have not been found to replicate in filamentous fungi (Fincham, 1989).

Mammalian Artificial Chromosomes

The controlled construction of mammalian artificial chromosomes (MACs) has been difficult because, with the exception of telomeres, the corresponding essential elements in mammals have not been fully defined. Higher eukaryotes (*e.g.*, mammals), in contrast to yeast, contain repetitive DNA sequences which form a boundary at both sides of the centromere. This highly repetitive DNA interacting with certain proteins, especially in animal chromosomes, creates a genetically inactive zone (heterochromatin) around the centromere. This pericentric heterochromatin keeps any selectable marker gene at a considerable distance, and thus repetitive DNA prevents the isolation of centromeric sequences by chromosome "walking." Alpha-satellite (alphoid) DNA forms a family of repeated DNA sequences found in amounts varying from 500 kb to 5 mb at the centromeres of human chromosomes. Alphoid sequences consist of a repeated 171 bp monomer that exhibits chromosome-specific variation in nucleotide sequence and higher order repeat arrangement.

U.S. Patent Number 5,288,625 reports that a cell line which contains a dicentric chromosome, one of the centromeres of which contains a segment of human DNA, can be treated so as to isolate the centromere which contains the human DNA on a chromosome away from other mammalian chromosomes. Using a mouse lung fibroblast cell which contains such a dicentric chromosome wherein the centromere is linked to a dominant selectable marker (*e.g.*, aminoglycoside-3' phosphotransferease-II), the inventor was able to isolate derivative cell lines which stably replicated a chromosome containing only centromeres comprising cloned human DNA.

Harrington *et al.* (1997) have constructed stable human artificial chromosomes by cotransfecting large synthetic arrays of alphoid repeats, telomere repeats, and random genomic DNA fragments into human cultured cells. In general, the resultant minichromosomes acquired host sequences by means of either a chromosome truncation event or rescue of an acentric fragment, but in one case minichromosome formation was by a *de novo* mechanism. The inclusion of uncharacterized genomic DNA in the transfection mixture raises the possibility that sequences other than the transfected alphoid and telomere DNA contributed to chromosome formation.

To construct YAC-based mammalian artificial chromosomes, Ikeno *et al.* (1998) introduced telomere repeats and selectable markers into a 100 kb YAC containing human centromeric DNA. The resultant YAC, which has regular repeat sequences of alpha-satellite DNA and centromere protein B (CENP-B) boxes, efficiently formed MACs that segregated accurately and bound CENP-B, CENP-C, and CENP-E. The MACs appear to be about 1-5 Mb in size and contain YAC multimers. It is not known whether the MACs are linear or circular. The data from structural analyses of the MACs by FISH and Southern blot hybridization suggest that the introduced YAC DNA itself must have been multimerized by recombination and/or amplification.

EXAMPLES

Example 1. Identification of a TERT Gene in *Plasmodium falciparum*.

Three segments of DNA containing portions of the putative *P. falciparum* TERT gene were identified by searching the Unfinished Microbial Genomes database (at the National Center for Biotechnology Information) via the "BLAST" algorithm.

Initially, the search utilized the following segment of the *Schizosaccharomyces pombe* TERT protein sequence in the region identified as the "T motif": FFYITESSDLRNRTVYFRKDIW (SEQ ID NO.11) (Linger *et al.*, 1997).

Two matches were found (Figure 1):

1. *P. falciparum* 3D7 unfinished sequence from chromosome 13 contig ID 41294 (3201 bp) from the Sanger Centre sequencing project; and

2. *P. falciparum* unfinished sequence from chromosome 14 contig 5560 (8833 bp) at The Institute for Genomic Research (TIGR).

A third match was found by searching the database using the following portion of the *S. pombe* C motif: LLRVVDDFLFITVNKKDAKKFLNLSLR (SEQ ID NO.12). The third clone was a 4190 bp contig from the Sanger Centre (*P. falciparum* 3D7 unfinished sequence from chromosome 13 contig 56572 (mal31p_02341) (Figure 1).

We discovered that the *P. falciparum* TERT gene was embedded in larger segments of chromosomal sequence which had not in any way been recognized or identified by the

sequencing projects that deposited the data.

The first two contigs (nos. 13-41294 and 14-5560) overlap to create ~10600 bp sequence including the entire putative *P. falciparum* TERT gene. The nucleotide sequence and corresponding amino acid sequence of the *P. falciparum* gene are presented in SEQ ID NO.5. The TERT protein sequence is provided in SEQ ID NO.6. The third contig (no. 13-56572) is a gene fragment that represents a second TERT gene in *P. falciparum*. Similarly, its nucleotide sequence and corresponding amino acid sequence appear in SEQ ID NOS. 7 and 8.

Sequence alignment of this ORF to TERT protein sequences of other organisms using Clustal® identified multiple regions of sequence similarity, showing that this protein is the *P. falciparum* TERT homolog (Figure 2).

The *Plasmodium* protein sequence contains the canonical reverse transcriptase motifs 1, 2, A, B', C, D and E, as well as the T motif possessed by all TERT proteins identified to date. The T motif in combination with the reverse transcriptase motifs has not been observed in any other proteins.

Variability exists for the amino acid sequence of the *P. falciparum* TERT gene. For example, we have found that residue 330 of SEQ ID NO.6 can also be Ile (*i.e.*, CTA=Leu in contig 5560 and ATA=Ile in contig 41294) Additionally, we have found that residue 335 can also be Gly (*i.e.*, GAT=Asp in contig 5560 and CTT=Gly in contig 41294). Other variations of SEQ ID NO.6 are certainly likely based on our findings and this invention encompasses all such natural and artificial variations in amino acid sequences as discussed herein.

Example 2. Reverse Transcription-PCR for Identified *P. falciparum* TERT Gene.

Total RNA prepared from *P. falciparum* was analyzed using reverse transcription coupled with the polymerase chain reaction (RT-PCR). DNA primers specific to the identified *Plasmodium* TERT gene were used to amplify two separate portions of the putative TERT mRNA. Control reactions were performed where reverse transcriptase was left out of the reaction to ensure signal did not arise from amplification of contaminating genomic DNA. See Figure 3 and accompanying text for electrophoresis methods and results.

P. falciparum RT-PCR primers are as follows:

PfRT 5' GTC ATC AAT AAA TCG GAG TAT GAG TG (SEQ ID NO.32);

pfTELfor 5' TTC TAA CCA AAT CTG AGC (SEQ ID NO. 33);

pfBREV 5' TGC ATA ATA TAG GGA GCA C (SEQ ID NO. 34);

pfRT2 5' CTTTTGCCATTCTCATATGAATATAC (SEQ ID NO. 35);

pfREV2 5' ATTATTATGACGTGTGATG (SEQ ID NO. 36);

pf2160 5' CATATAATTACATCGAGG (SEQ ID NO. 37).

The RT-PCR process was repeated with two different primer sets amplifying different parts of the TERT gene. Results show that the TERT gene is indeed functional and not a pseudogene, as most transcribed protein genes are also translated into functional proteins.

Example 3. Identification of a Gene Fragment for a *P. falciparum* TERT Gene.

In addition to the full length *P. falciparum* TERT gene of SEQ ID NO.5, we have identified a TERT gene fragment which represents a second TERT gene in *P. falciparum* (SEQ ID NO.7).

Protein translation of the second TERT gene (794 amino acids, corresponding to amino acids 1392 to 2184 of full length *P. falciparum* TERT) shows that there are 9 base changes as compared to the full length TERT sequence, resulting in 7 amino acid changes (amino acid numbers refer to the full length sequence):

1398 Ser to Gly

1399 Val to Ala

1614 Phe to Ser

1777 Ile to Asn

1870 Ser to Thr

1884 Leu to Val

1928 His to Gln.

Example 4. Identification of TERT Genes in *Candida albicans*.

A segment of DNA containing a potential *Candida albicans* TERT gene was identified by searching the Unfinished Microbial Genomes database (at the National Center for

Biotechnology Information) via the "BLAST" algorithm. The search utilized a segment of the *S. pombe* TERT protein sequence in the region identified as the "T motif" (Nakamura *et al.*, 1997) [sequence WLYNS...CRPFIT, SEQ ID NO.11] compared to the eukaryotes database with the Expect parameter at 100.

The third match, with a match score of 34, was contig 3-3463 from the *C. albicans* sequencing project at the Stanford Sequencing and Technology Center. Contig 3-3463 is a 11961 base pair genomic fragment.

By taking the complement of the strand as obtained from the database, base pairs 144-2747 of the contig form an open reading frame (ORF) of 867 amino acids.

Additional work demonstrated that there were two different genes within a single *C. albicans* cell that both coded for TERT genes. This is the first such report of two TERT genes within a single cell or for two different TERT genes identified in a single organism. The existence of two TERT genes suggests that they different functions.

The two *C. albicans* TERT genes differ at 12 base pairs, 7 that are silent, and 5 that cause amino acid changes. Additionally, there are 7 residues in each gene (amino acid positions # 114, 452, 487, 538, 634, 735, and 856) that are encoded by a CTG (CUG) codon that would normally be Leu, but are Ser in *Candida*. *C. albicans* is one of several *Candida* species that have an unusual tRNA that charges Ser onto the tRNA that reads CUG codons.

The nucleotide sequences and corresponding amino acid sequences of the two *C. albicans* genes are presented in SEQ ID NOs: 1 and 3. The corresponding TERT protein sequences are provided in SEQ ID NOs: 2 and 4, respectively.

Sequence alignment of this ORF to TERT protein sequences of other organisms using Clustal® identified multiple regions of sequence similarity, showing that this protein is the *Candida* TERT homolog (Figure 2).

The *Candida* protein sequence contains the canonical reverse transcriptase motifs 1,2, A, B', C, D and E, as well as the T motif possessed by all TERT proteins identified to date. Besides these motifs, many other regions of sequence similarity are present between this and other TERT genes. The T motif in combination with the reverse transcriptase motifs has not been observed in any other proteins.

Example 5. Reverse Transcription-PCR for Identified *C. albicans* TERT Genes.

Total RNA prepared from log phase *C. albicans* cells was analyzed using reverse transcription coupled with the polymerase chain reaction (RT-PCR). DNA primers specific to the identified *Candida* TERT genes were used to amplify four separate portions of the TERT mRNA.

The QIAGEN® Genomic Tip-100 Kit was used for the genomic DNA isolation procedure. The protocol for yeast was utilized as set forth in the QIAGEN® handbooks and protocols for the use of the kits (http://www/qiagen.com/literature/handbooks/index.html; QIAGEN® Genomic DNA Handbook 9/97 (PDF version, 224 KB)).

Briefly, *C. albicans* is inoculated into 50 ml GYEP media (glucose 2%, peptone 1%, yeast extract 0.3%) and grown overnight at 37C with shaking. Cells are washed with buffer Y1 (1M sorbitol, 0.1 M EDTA, pH 7.4) and incubated with buffer Y1 plus 0.1%beta mercaptoethanol, 50 units lyticase (zymolase) per 10^7 cells for 1 h at 30C to break down cell walls. Spheroplasts are harvested by centrifugation at 300x g. The spheroplasts are then lysed, and run over the DNA binding columns, and the genomic DNA is washed on the column and eluted according to the manufacturer's instructions using the buffers provided by the manufacturer.

C. albicans RTPCR primers:

CaRT1 CAGGGGGTATTGAAGAGATAGAAGCAGCG (SEQ ID NO.13);
CaFor1 TCGTTGTTATTCACGCGTATCG (SEQ ID NO.14);
CaNEST1 GCGACAATTGAGAGATATCGAG (SEQ ID NO.15);
CaRT2 GCACTTGATCATAAATATTCGAATCGGGGCG (SEQ ID NO.16);
CaFOR2 TTATGGAAAGAGCTATACG (SEQ ID NO.17);
CaNEST2 TGAGAATCCCTGAAACACG (SEQ ID NO.18);
CaRT3 CAATTTATGTGAACGCGTCCAACTGAGCGTAG (SEQ ID NO.19);
CaFOR3 GATACGACATTCTATATGC (SEQ ID NO.20);
CaNEST3 TCAATACAGGTTGGCTGAG (SEQ ID NO.21).

We also used custom primers for sequencing the internal regions of the gene. They include the RTPCR primers listed above as well as the following:

CaFor480 5' TATTTCTGTTACTCGGACCA (SEQ ID NO.22);
CaFor1620 5' AGAGACTCCTTGTTAACC (SEQ ID NO.23);
CaFor1980 5' CAGTTAAAGATGCACGAGG (SEQ ID NO.24);
CaFor2310 5' TGAATAACAACAGATCTAAGC (SEQ ID NO.25);
CaFor2630 5' CAGCGACTGGGATGGTGC (SEQ ID NO.26);
CaRev290 5' ATTCTTGTGGTCGAATCGC (SEQ ID NO.27);
CaRev630 5' TAAAGCACATTGAATTTGG (SEQ ID NO.28);
CaRev1030 5' TAAATCATCCATATGTATC (SEQ ID NO.29);
CaRev1380 5' TAACACGAAAGCTCGAGCG (SEQ ID NO.30);
CaRev2340 5' AAACTTATCAGACCGGAG (SEQ ID NO.31).

Control reactions were performed where reverse transcriptase was left out of the reaction to ensure signal did not arise from amplification of contaminating genomic DNA. See Figure 4 and accompanying text for electrophoresis methods and results.

A second RT-PCR was conducted using four *C. albicans* RT-PCR reactions, controls, and the same reactions done in genomic DNA described above. See Figure 5 for overview of the procedures and the resultant gel.

Results show that the TERT gene is indeed functional and not a pseudogene, as most transcribed protein genes are also translated into functional proteins.

Example 6. Identification of Two TERT Genes in Strain 3153 of *C. albicans*.

Two overlapping PCR products, P1 and P2, representing the entire coding region of the TERT gene, were amplified from genomic DNA from *C. albicans* strain 3153 (serotype A). P1 was amplified using primers CaRTfor1 and CaRT3, and P2 was amplified using primers CaFor2 and CaRT. The reaction conditions were 40 cycles of 1 min. at 94C, 1 min. at 52C and 3 min. at 68C, followed by a final 6 min incubation at 68C. The resulting PCR products were gel purified and sequenced on both strands using internal primers specific to *C. albicans* strain 3153 (serotype A).

RT- PCR was used to produce four overlapping PCR products, P1, P2, P3 and P4. These are the same four products described in the RT-PCR experiment used to determine if the

TERT gene is transcribed (see above). RT-PCR was performed using the Access RT-PCR kit (Promega®). For all RT-PCR reactions, a negative control was done (no reverse transcriptase added) to ensure that products were indeed amplified from RNA and not potential contaminating genomic DNA. The resulting PCR products were gel purified and sequenced on both strands using internal primers specific to the *Candida albicans* TERT twelve sites on the gene where the data was ambiguous. At these locations, electropherogram data from both strands showed two overlapping peaks, making identification of the proper nucleotide at that position impossible. This did not appear to be an artifact of the sequencing reactions, as data on both sides of the nucleotide in question was of high quality and unambiguous, with data on both strands in agreement as to the nucleotide sequence. Additionally, the same sites were identified as ambiguous in sequencing the genomic DNA PCR products and the RT-PCR products derived from the RNA.

Comparison of the PCR products derived from the genomic DNA and the total cellular RNA also proves that there are no intron sequences in the *Candida* TERT gene. To prove that the overlapping peaks on the sequencing electropherograms were due to simultaneous amplification of multiple sequences, three RT-PCR products, P1, P2 and P5 (amplified with primers Ca480For and CaRT2) were cloned into the pGEM-T vector and individual clones were sequenced. The three overlapping pieces were utilized because the entire gene could not be amplified by PCR in one piece. The three pieces, however, overlap significantly. Of the 2601 base pairs that comprise the coding region, P1 spans bases 1-1659, P2 spans bases 1108-2601 and P5 spans bases 335-2047. Since only one amplicon is ligated into each vector, individual amplicons could be sequenced. Five P1, six P2 and two P5 clones were sequenced. At sites that had showed two overlapping base peaks on the electropherograms when PCR products were sequenced, clones would have either one or the other of the two bases. In this manner, the clones sorted into two classes, which when overlapped, generate the entire coding sequence of two genes, CaTERT1 and CaTERT2. These two genes differ at twelve positions, resulting in seven silent changes (that is, the two triplet codons designate the same amino acid) and five amino acid differences between the two proteins.

Example 7. Identification of Two TERT Genes in Strain 3153 of *C. albicans*.

The TERT gene of another *Candida albicans* strain, 9938, was also amplified in two overlapping PCR products, P1 and P2, as was done with strain 3153(A). The PCR products were sequenced on both strands in the same manner as strain 3153(A). The sequence data clearly indicates that this strain also has two TERT genes, which are different from the two TERT genes found in strain 3153(A) (SEQ ID NOs.1 and 3, respectively).

Of the twelve differing sites in 3153(A), three are unambiguous in the sequencing data for strain 9938, while four sites that are identical in both genes of strain 3153(A) appear to differ in the two genes of strain 9938.

The sequences of strain 9938 match those of SEQ ID NOs.1 and 3 for *C. strain* 3153(A) except for the following changes as indicated below:

1. Position 1131 is always C, thus always Ser for the amino acid (rather than C or T in 3153A);

2. Position 2185 is always A, thus always Thr for the amino acid (rather than A or C in 3153A);

3. Position 2209 is always T (rather than T or C in 3153A). amino acid is identical either way;

4.. Position 2445, is either T or C (rather than always T in 3153A). Amino acid is Val or Asp (rather than always Val in 3153A);

5. Position 2485, is either T orC (only T in 3153A). amino acid is Phe either way;

6. Position 1927 is either T or C (only C in 3153A), amino acid is identical; and

7. Position 2036 is either A or G (only G (Val) in 3153A). Amino acid is thus either Ile or Val.

Example 8. Identification of a TERT Gene Fragment in *Oryza sativa*.

A segment of DNA containing a potential *Oryza sativa* TERT gene was identified by first searching the *Arabidopsis thaliana* database (at the Stanford University DNA Sequence and Technology Development Center home page, *www-sequence.stanford.edu*) via the "BLAST" algorithm. The search utilized a segment of the *Arabidopsis* TERT protein sequence in the

region identified as the "C motif" (sequence WLYNS...CRPFIT) compared to the higher plant sequence database with the Expect parameter at 100.

The second match, with a match score of 74, was accession number AQ510589 from the *O. sativa* sequencing project at Clemson University. AQ510589 is a 531 base pair genomic fragment.

The BAC containing the sequence fragment of interest was obtained from Clemson University and resequenced. The sequences of the primers used for this process are (Note: K is G+T):

Rice ep-2for: 5'CCT KAA TAT TTK TTA ATK AKK (SEQ ID NO.38);

Rice er-rev 5' KTC ATA CCT CKT ATA ATC AKC (SEQ ID NO.39).

These primers are degenerate because they can also be used for *Arabidopsis*.

The nucleotide sequence and corresponding amino acid sequence of the *O. sativa* gene is presented in SEQ ID NO.9. The TERT protein sequence is provided in SEQ ID NO.10.

Sequence alignment of this ORF to the TERT nucleotide sequence of *Arabidopsis thaliana* (SEQ ID NO:48) identified multiple regions of sequence similarity, showing that this protein is the *O sativa* TERT homolog (Figure 6). The *O. sativa* protein sequence contains the canonical reverse transcriptase motifs C, D and E.

Example 9. Reverse Transcription-PCR for Identified *O. sativa* TERT Gene. Fragment

Total RNA prepared from *O sativa* was analyzed using reverse transcription coupled with the polymerase chain reaction (RT-PCR) using the methods described above. DNA primers specific to the identified *Oryza* TERT gene were used to amplify separate portions of the putative TERT mRNA. Control reactions were performed where reverse transcriptase was left out of the reaction to ensure signal did not arise from amplification of contaminating genomic DNA.

Results show that the TERT gene fragment is indeed functional and not a pseudogene, as most transcribed protein genes are also translated into functional proteins.

Example 10. Use of the *O. sativa* TERT Gene Fragment as a Probe to Isolate TERT Genes from Plants.

The isolation of *O. sativa* TERT genes, TERT genes from other plant species, and related genes, such as TERT promoters, may be accomplished by a number of techniques. For instance, oligonucleotide probes based on the sequences disclosed herein can be used to identify the desired gene in a cDNA or genomic DNA library. To construct genomic libraries, large segments of genomic DNA are generated by random fragmentation, *e.g.* using restriction endonucleases, and are ligated with vector DNA to form concatemers that can be packaged into the appropriate vector. cDNA may be prepared from mRNA extracted from any rice cells in which TERT genes or homologs are expressed.

The cDNA or genomic library can then be screened using a probe based upon the rice TERT gene fragment of SEQ ID NO.9. Such a probe may include the entire sequence of SEQ ID NO.9 or a portion or fragment of this sequence. The probe may be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different plant species.

Alternatively, the nucleic acids of interest can be amplified from nucleic acid samples using amplification techniques. For instance, polymerase chain reaction (PCR) technology to amplify the sequences of the TERT gene and related genes directly from genomic DNA, from cDNA, from genomic libraries or cDNA libraries. PCR and other *in vitro* amplification methods may also be useful, for example, to clone nucleic acid sequences that code for proteins to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes.

Appropriate primers and probes for identifying TERT sequences from plant tissues are generated from comparisons of the sequences provided herein for rice. For a general review of PCR see Gelfand et al., 1990, *PCR Protocals: A Guide to Methods and Applications* (Academic Press, San Diego).

The foregoing detailed description has been given for clearness of understanding only and no unnecessary limitations should be understood therefrom as modifications will be obvious to those skilled in the art.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth and as follows in the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule selected from the group consisting of: (a) an isolated nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (b) an isolated nucleic acid molecule that encodes a fragment of at least 6 amino acids of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (c) an isolated nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule comprising SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9 under conditions of sufficient stringency to produce a clear signal; and (d) an isolated nucleic acid molecule which hybridizes to a nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 under conditions of sufficient stringency to produce a clear signal.

2. The isolated nucleic acid molecule of claim 1, wherein the nucleic acid molecule comprises the sequence of SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9.

3. The isolated nucleic acid molecule of claim 2, wherein the nucleic acid molecule consists of the sequence of SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.7 or SEQ ID NO.9.

4. The isolated nucleic acid molecule of any one of claims 1-3, wherein said nucleic acid molecule is operably linked to one or more expression control elements.

5. A vector comprising an isolated nucleic acid molecule of any one of claims 1-3.

6. A host cell transformed to contain the nucleic acid molecule of any one claims 1-3.

7. A host cell comprising a vector of claim 5.

8. A method for producing a polypeptide comprising the step of culturing a host cell transformed with the nucleic acid molecule of any one of claims 1-3 under conditions in which the protein encoded by said nucleic acid molecule is expressed.

9. An isolated polypeptide produced by the method of claim 8.

10. An isolated polypeptide selected from the group consisting of: (a) an isolated polypeptide comprising the amino acid sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (b) an isolated polypeptide comprising a fragment of at least 6 amino acids of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; (c) an isolated polypeptide comprising conservative amino acid substitutions of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10; and (d) naturally occurring amino acid sequence variants of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

11. An isolated antibody that binds to a polypeptide of either claim 9 or 10.

12. The antibody of claim 11 wherein said antibody is a monoclonal or polyclonal antibody.

13. A method of identifying an agent which modulates the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the steps of:

exposing cells which express the nucleic acid to the agent; and

determining whether the agent modulates expression of said nucleic acid, thereby identifying an agent which modulates the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ

ID NO.10.

14. A method of identifying an agent which modulates at least one activity of a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the steps of:

exposing cells which express the protein to the agent;

determining whether the agent modulates at least one activity of said protein, thereby identifying an agent which modulates at least one activity of a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

15. A method of identifying binding partners for a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10, comprising the steps of:

exposing said protein to a potential binding partner; and

determining if the potential binding partner binds to said protein, thereby identifying binding partners for a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

16. A method of modulating the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the step of:

administering an effective amount of an agent which modulates the expression of a nucleic acid encoding the protein having the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

17. A method of modulating at least one activity of a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10 comprising the step of:

administering an effective amount of an agent which modulates at least one activity of

a protein comprising the sequence of SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.8 or SEQ ID NO.10.

18. A method for diagnosing *Plasmodium falciparum* infection in a patient comprising the steps of:

obtaining a cell sample from the patient;

determining whether the nucleic acid of SEQ ID NO.5 or SEQ ID NO.7 or the protein of SEQ ID NO.6 or SEQ ID NO.8 is present within the cell sample; and

correlating the presence of the nucleic acid of SEQ ID NO.5 or SEQ ID NO.7 or the protein of SEQ ID NO.6 or SEQ ID NO.8 with the presence of *Plasmodium falciparum*.

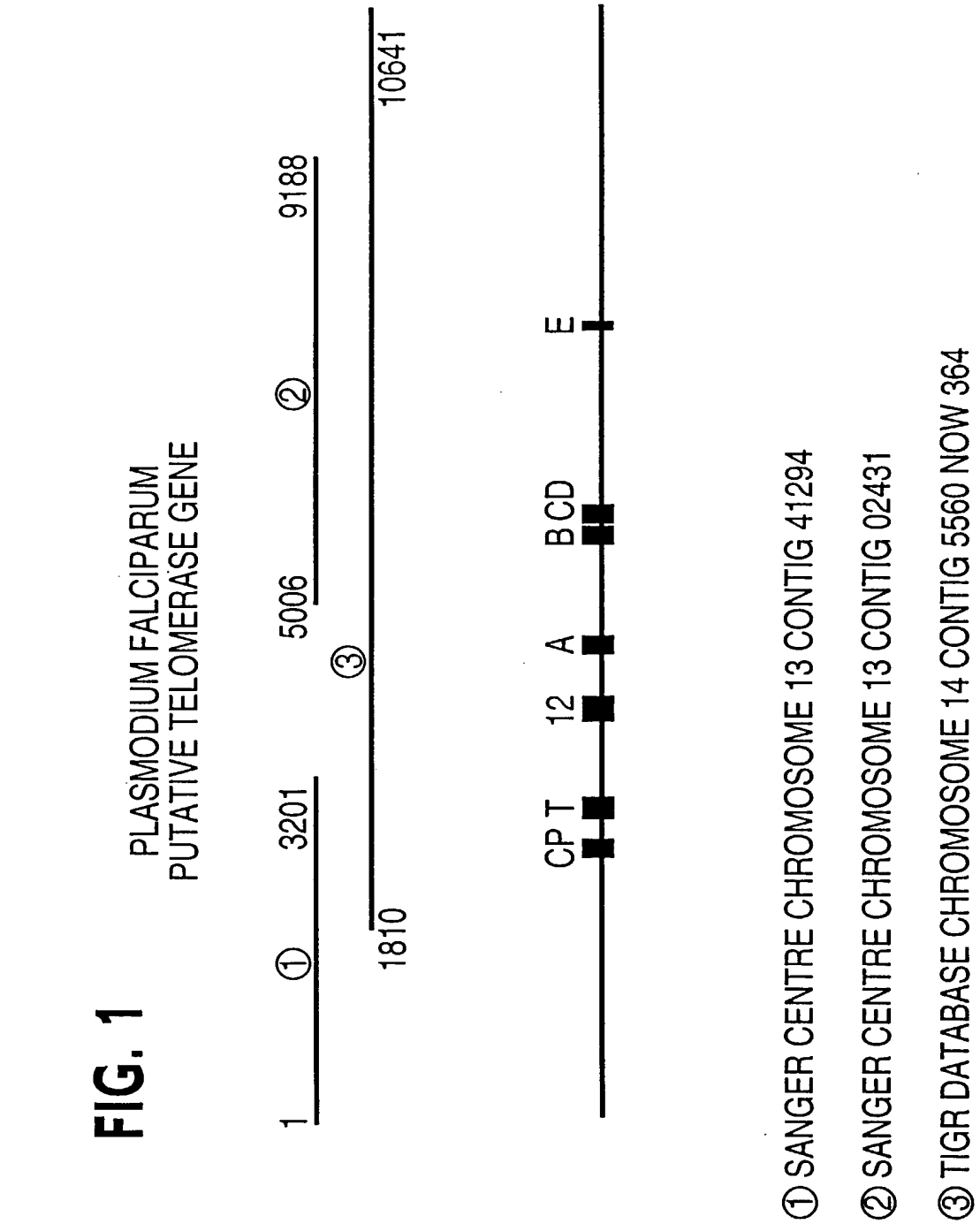
19. A method for diagnosing *Candida albicans* infection in a patient comprising the steps of:

obtaining a cell sample from the patient;

determining whether the nucleic acid of SEQ ID NO.1 or SEQ ID NO.3 or the protein of SEQ ID NO.2 or SEQ ID NO.4 is present within the cell sample; and

correlating the presence of the nucleic acid of SEQ ID NO.1 or SEQ ID NO.3 or the protein of SEQ ID NO.2 or SEQ ID NO.4 with the presence of *Candida albicans*.

FIG. 1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CP T
12
A
B CD
E
① SANGER CENTRE CHROMOSOME 13 CONTIG 41294
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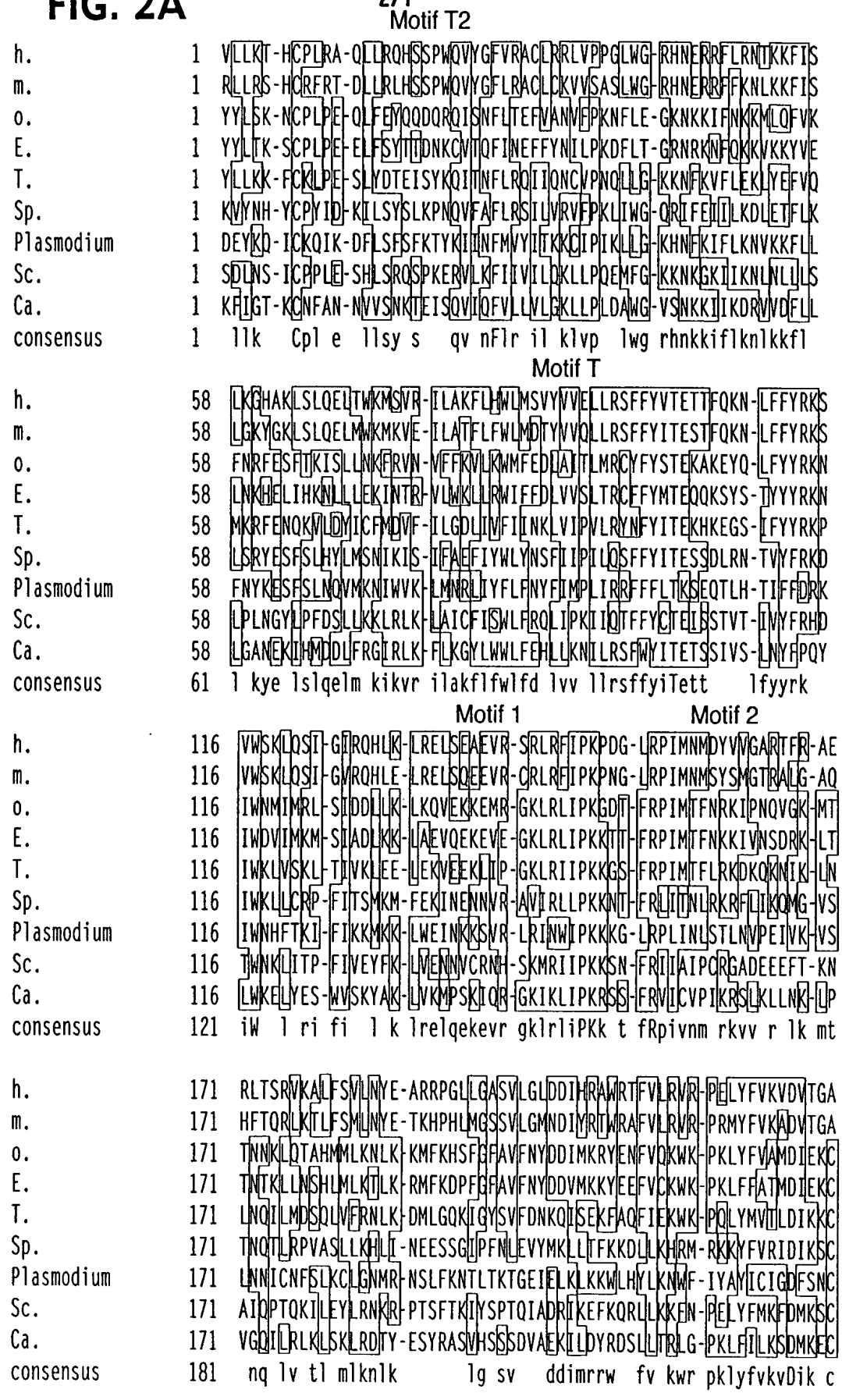
FIG. 2A


Motif T2
Motif T
Motif 1
Motif 2
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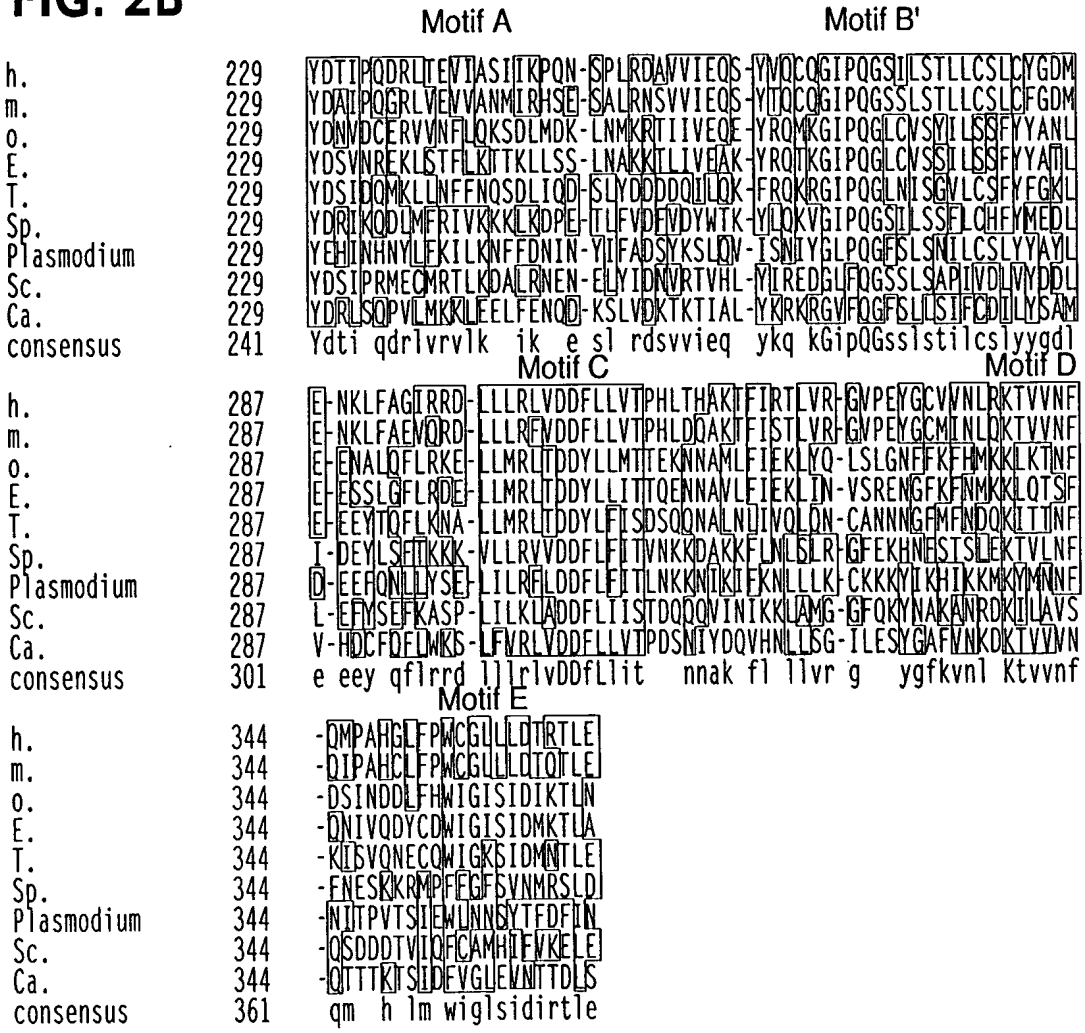
m.
o.
E.
T.
Sp.
Plasmodium
Sc.
Ca.
consensus

FIG. 2B


Motif A
Motif B'
Motif C
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m. 229 YDAIPQGRLVEVVANMIRHSE-SALRNSVVIEQS-YTQCQGIPQGSSLSTLLCSLCFGDM
o. 229 YDNVDCERVVNFLQKSDLMDK-LNMKRTIIVEQE-YRQMKGIPQGLCVSSVILSSFYYANL
E. 229 YDSVNREKLSTFLKTTKLLSS-LNAKKTLIVEAK-YRQTKGIPQGLCVSSILSSFYYATL
T. 229 YDSIDQMKLLNFFNQSDLIQD-SLYDDDDQILQK-FRQKRGIPQGLNISGVLCSFYFGKL
Sp. 229 YDRIKQDLMFRIVKKKLKDPE-TLFVDFVDYWIK-YLQKVGIPQGSILSSFLCHFYMEDL
Plasmodium 229 YEHINHNYLFKILKNFFDNIN-YIFADSYKSLQV-ISNIYGLPQGFSLSNILCSLYYAYL
Sc. 229 YDSIPRMECMRTLKDALRNEN-ELYIDNVRTVHL-YIREDGLFQGSSLSAPIVDLVYDDL
Ca. 229 YDRLSQPVLMKKLEELFENQD-KSLVDKTKTIAL-YKRKRGVFQGFSLLSIFCDILYSAM
consensus 241 Ydti qdrlvrvlk ik e sl rdsvvieq ykq kGipQGsslstilcslyygdl
h. 287 E-NKLFAGIRRD-LLLRLVDDFLLVTPHLTHAKTFIRTLVR-GVPEYGCVVNLRKTVVNF
m. 287 E-NKLFAEVQRD-LLLRFVDDFLLVTPHLDQAKTFISTLVR-GVPEYGCMINLQKTVVNF
o. 287 E-ENALQFLRKE-LLMRLTDDYLLMTTEKNNAMLFIEKLYQ-LSLGNFFKFHMKKLKTNF
E. 287 E-ESSLGFLRDE-LLMRLTDDYLLITTQENNAVLFIEKLIN-VSRENGFKFNMKKLQTSF
T. 287 E-EEYTQFLKNA-LLMRLTDDYLFISDSQQNALNLIVQLQN-CANNNGFMFNDQKITTNF
Sp. 287 I-DEYLSFTKKK-VLLRVVDDFLFITVNKKDAKKFLNLSLR-GFEKHNFSISLEKTVLNF
Plasmodium 287 D-EEFQNLLYSE-LILRFLDDFLFITLNKKNIKIFKNLLLK-CKKKYIKHIKKMKYMNNF
Sc. 287 L-EFMSEFKASP-LILKLADDFLIISTDQQQVINIKKLAMG-GFQKYNAKANRDKILAVS
Ca. 287 V-HDCFDFLWKS-LFVRLVDDFLLVTPDSNIYDQVHNLLSG-ILESYGAFVNKDKTVVVN
consensus 301 e eey qflrrd lllrlvDDfLlit nnak fl llvr g ygfkvnl Ktvvnf
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m. 344 -QIPAHCLFPWCGLLLQTQTLE
o. 344 -DSINDDLFHWIGISIDIKTLN
E. 344 -QNIVQDYCDWIGISIDMKTLA
T. 344 -KISVQNECQWIGKSIDMNTLE
Sp. 344 -FNESKKRMPFFGFSVNMRSLD
Plasmodium 344 -NITTPVTSIEWLNNSYTFDFIN
Sc. 344 -QSDDDTVIQFCAMHIFVKELE
Ca. 344 -QTTTKTSIDFVGLEVNTTDLS
consensus 361 qm h lm wiglsidirtle

FIG. 3

TERT RTPCR ON TOTAL RNA OF *Plasmodium falciparum*

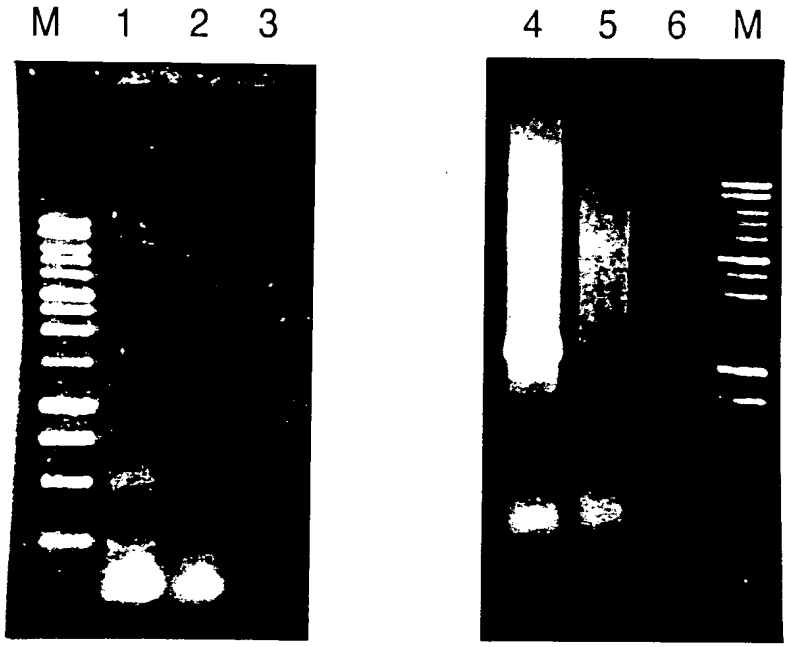


FIG. 4

RT-PCR ON TOTAL RNA OF *Candida albicans*

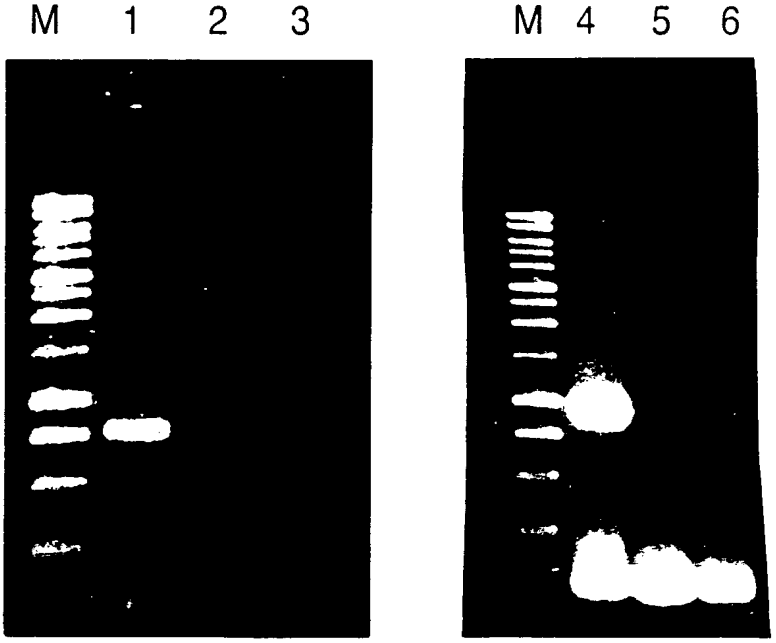
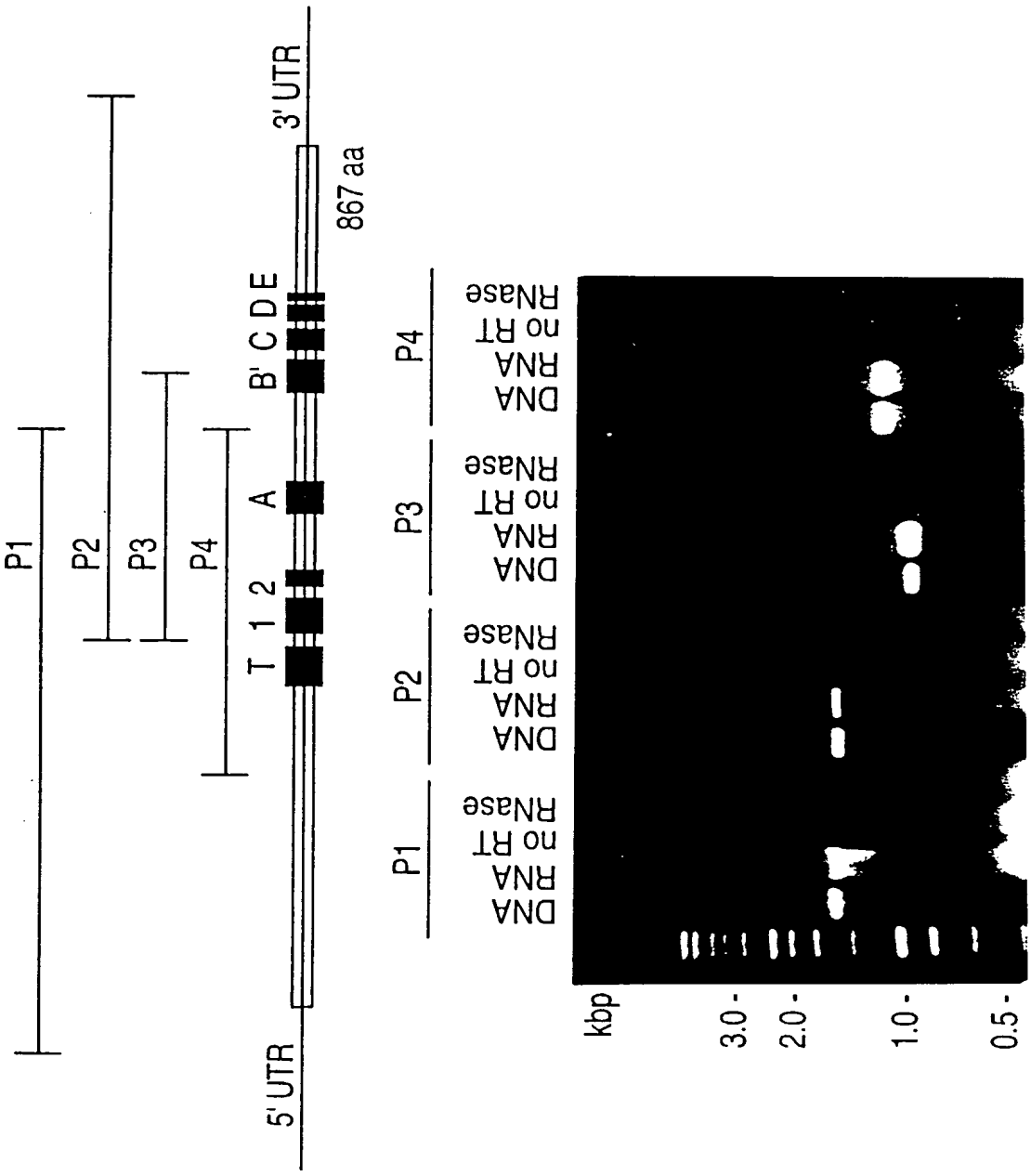


FIG. 5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P2
P3
P4
5' UTR
T 1 2 A B' C D E
3' UTR
867 aa
P1
P2
P3
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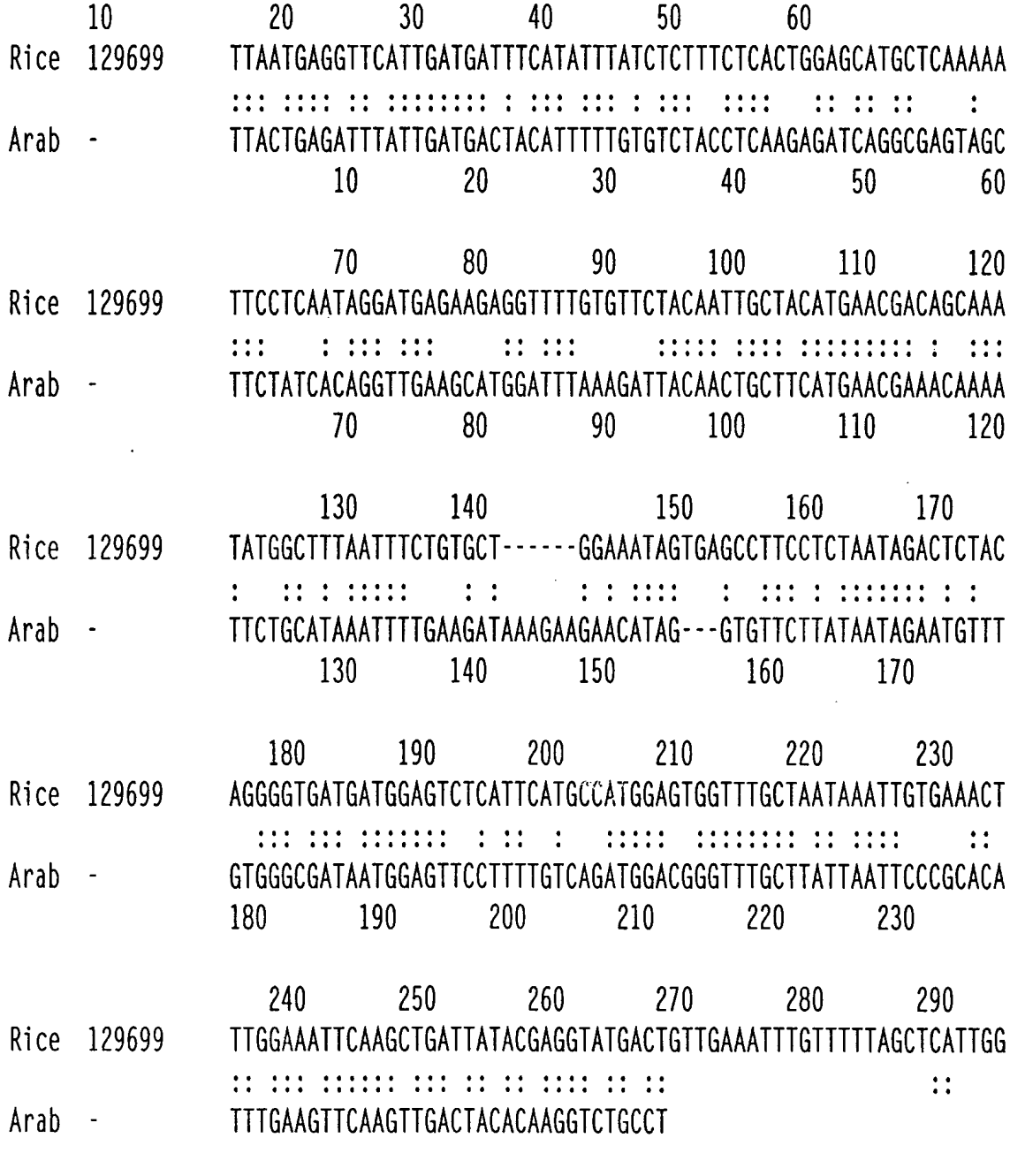
RNA
no RT
RNase
kbp
3.0 -
2.0 -
1.0 -
0.5 -

FIG. 6



ALIGNMENT: RICE-ARABIDOPSIS NUCLEOTIDE SEQUENCE.

SEQUENCE LISTING

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Love, Ruschelle A.
Long, David M.
Research and Development Institute, Inc.

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735 and 856 are translated as Ser in C. albicans,
not as Leu (from ctg codons).

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Met Thr Val
1

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Lys Val Asn Glu Lys Lys Thr Leu Leu Gln Tyr Val Leu Asp Asn Thr
5 10 15

agc aat gac gtg cca ttg cta cct agt ttg aaa gag tac atg gag acg 154
Ser Asn Asp Val Pro Leu Leu Pro Ser Leu Lys Glu Tyr Met Glu Thr
20 25 30 35

gtg ctt gta tac aaa tcc ata aaa cgg cct cta cca gcg att cga cca 202
Val Leu Val Tyr Lys Ser Ile Lys Arg Pro Leu Pro Ala Ile Arg Pro
40 45 50

caa gaa tca ttt gac gaa ttt atg aaa gag ttg gtg acc cgt tta gtt 250

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Gln Glu Ser Phe Asp Glu Phe Met Lys Glu Leu Val Thr Arg Leu Val
             55                  60                  65

atg gaa aaa tcg aat aat gtt ata gct tat ggg tat aag act tct gca   298
Met Glu Lys Ser Asn Asn Val Ile Ala Tyr Gly Tyr Lys Thr Ser Ala
         70                  75                  80

atg gag agt cga agt ata ttt aca acg ttt cat tcg agt ggg aat ttt   346
Met Glu Ser Arg Ser Ile Phe Thr Thr Phe His Ser Ser Gly Asn Phe
     85                  90                  95

att tta act cac att aca agc cat aac tgg agt aca ata ttt ctg tta   394
Ile Leu Thr His Ile Thr Ser His Asn Trp Ser Thr Ile Phe Leu Leu
100                 105                 110                 115

ctc gga cct aaa aaa ttt cta gag cta tta gtt aat aat aag ggg ttt   442
Leu Gly Pro Lys Lys Phe Leu Glu Leu Leu Val Asn Asn Lys Gly Phe
                120                 125                 130

gtt agt aag gtg aat ggt gaa tct gtg caa ata ttc ggt gac gtg aac   490
Val Ser Lys Val Asn Gly Glu Ser Val Gln Ile Phe Gly Asp Val Asn
            135                 140                 145

tct cac aga aag gct gtc gtc gtt tcc aaa tac att acc aaa ttc aat   538
Ser His Arg Lys Ala Val Val Val Ser Lys Tyr Ile Thr Lys Phe Asn
        150                 155                 160

gtg ctt tac aac tcc tat tcc agg gac ttc tca cgc ttt gag atg ata   586
Val Leu Tyr Asn Ser Tyr Ser Arg Asp Phe Ser Arg Phe Glu Met Ile
    165                 170                 175

aga ccc agt att caa act ata tta cag gat att ctt tcc ttt tct ggt   634
Arg Pro Ser Ile Gln Thr Ile Leu Gln Asp Ile Leu Ser Phe Ser Gly
180                 185                 190                 195

ttg aat cct gga aga tca tct aaa aga tat cga ggc ttc aaa agt ttg   682
Leu Asn Pro Gly Arg Ser Ser Lys Arg Tyr Arg Gly Phe Lys Ser Leu
                200                 205                 210

ctc tcg aga att att gct aat gat aag aaa tgt aga tac gac att cta   730
Leu Ser Arg Ile Ile Ala Asn Asp Lys Lys Cys Arg Tyr Asp Ile Leu
            215                 220                 225

tat gct aag ttt att ggt acg tca aaa tgc aat ttt gct aat gtg gtg   778
Tyr Ala Lys Phe Ile Gly Thr Ser Lys Cys Asn Phe Ala Asn Val Val
        230                 235                 240

agt aat aag aca gaa ata tcc cag gta att caa ttt gta ctt tta gta   826
Ser Asn Lys Thr Glu Ile Ser Gln Val Ile Gln Phe Val Leu Leu Val
    245                 250                 255

ttg ggt aaa ttg tta cct ttg gat gct tgg gga ggt gtt tcc aat aaa   874
Leu Gly Lys Leu Leu Pro Leu Asp Ala Trp Gly Gly Val Ser Asn Lys
260                 265                 270                 275

aag att att aag gac cga gtg gta gat ttt ttg tta ctt ggg gca aat   922
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Lys Ile Ile Lys Asp Arg Val Val Asp Phe Leu Leu Leu Gly Ala Asn
                280                 285                 290

gaa aag ata cat atg gat gat tta ttt aga gga att aga cta aaa gat   970
Glu Lys Ile His Met Asp Asp Leu Phe Arg Gly Ile Arg Leu Lys Asp
            295                 300                 305

ttc aag tgg ttg ggc aga gct cac caa att tct tcg aaa caa gat ttc  1018
Phe Lys Trp Leu Gly Arg Ala His Gln Ile Ser Ser Lys Gln Asp Phe
        310                 315                 320

gag ctc cga aca gct ttt cta aaa ggg tat cta tgg tgg ttg ttt gaa  1066
Glu Leu Arg Thr Ala Phe Leu Lys Gly Tyr Leu Trp Trp Leu Phe Glu
    325                 330                 335

cat tta ctt aaa aat att ctc cgt tct ttc tgg tac att act gaa act  1114
His Leu Leu Lys Asn Ile Leu Arg Ser Phe Trp Tyr Ile Thr Glu Thr
340                 345                 350                 355

tca agt ata gtg agt tca gag ttg aat tat ttt cct cag tat tta tgg  1162
Ser Ser Ile Val Ser Ser Glu Leu Asn Tyr Phe Pro Gln Tyr Leu Trp
                360                 365                 370

aaa gag cta tac gag tca tgg gtg tct aaa tat gca aag aat aat ctt  1210
Lys Glu Leu Tyr Glu Ser Trp Val Ser Lys Tyr Ala Lys Asn Asn Leu
            375                 380                 385

gtg aaa atg cca tca aag atc caa aga gaa caa cta cca tgt ggg aaa  1258
Val Lys Met Pro Ser Lys Ile Gln Arg Glu Gln Leu Pro Cys Gly Lys
        390                 395                 400

att aaa ctc ata ccc aag cgc tcg agc ttt cgt gtt att tgt gta cct  1306
Ile Lys Leu Ile Pro Lys Arg Ser Ser Phe Arg Val Ile Cys Val Pro
    405                 410                 415

ata aaa cga tcc ttg aaa cta ttg aac aaa aaa ttg gaa ttg gac aca  1354
Ile Lys Arg Ser Leu Lys Leu Leu Asn Lys Lys Leu Glu Leu Asp Thr
420                 425                 430                 435

ttg gaa aag gag aaa agg gaa ttt gaa agg tac aga aaa gag gtt tta  1402
Leu Glu Lys Glu Lys Arg Glu Phe Glu Arg Tyr Arg Lys Glu Val Leu
                440                 445                 450

ctg cca gtg gga caa ata cta cgc ttg aaa tta tcg aaa cta aga gat  1450
Leu Pro Val Gly Gln Ile Leu Arg Leu Lys Leu Ser Lys Leu Arg Asp
            455                 460                 465

aca tat gaa agc tat agg gct tca gta cat tcc agt tct gat gtg gct  1498
Thr Tyr Glu Ser Tyr Arg Ala Ser Val His Ser Ser Ser Asp Val Ala
        470                 475                 480

gaa aag ata ctg gat tat aga gac tcc ttg tta acc aga ttt ggc gaa  1546
Glu Lys Ile Leu Asp Tyr Arg Asp Ser Leu Leu Thr Arg Phe Gly Glu
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atc cct aag ctt ttc atc tta aag ttt gac atg aaa gaa tgt tat gat  1594
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Ile Pro Lys Leu Phe Ile Leu Lys Phe Asp Met Lys Glu Cys Tyr Asp
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Arg Leu Ser Gln Pro Val Leu Met Lys Lys Leu Glu Glu Leu Phe Glu
                520                 525                 530

aac caa gat aat aag act ctg tat tat gtt cga tac tac gct cag ttg   1690
Asn Gln Asp Asn Lys Thr Leu Tyr Tyr Val Arg Tyr Tyr Ala Gln Leu
            535                 540                 545

gac gcg tca cat aaa ttg aaa aaa gtg aaa acc act ata gat acc cag   1738
Asp Ala Ser His Lys Leu Lys Lys Val Lys Thr Thr Ile Asp Thr Gln
        550                 555                 560

tat cac aat tta aac att ttg tcg agc tca agg cat ctc agt aat tgt   1786
Tyr His Asn Leu Asn Ile Leu Ser Ser Ser Arg His Leu Ser Asn Cys
    565                 570                 575

aaa tct ttg gtc gat aag acc aag aca ata gcg ttg caa aaa ggt aac   1834
Lys Ser Leu Val Asp Lys Thr Lys Thr Ile Ala Leu Gln Lys Gly Asn
580                 585                 590                 595

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    645                 650                 655

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660                 665                 670                 675

tcg aat att tat gat caa gtg cac aat ata tta tca gga aaa ata ctt   2122
Ser Asn Ile Tyr Asp Gln Val His Asn Ile Leu Ser Gly Lys Ile Leu
                680                 685                 690

gag agc tat gga gct ttt gtt aat aaa gat aaa aca gtc gtt gtt aat   2170
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            695                 700                 705

caa aca acc acg aaa aca agt ata gat ttc gtt ggg ctt gaa gtg aat   2218
Gln Thr Thr Thr Lys Thr Ser Ile Asp Phe Val Gly Leu Glu Val Asn
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aca aca gat cta agc atc aaa agg aac tcc ggt ctg ata agt ttg gtt   2266
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Thr Thr Asn Phe Arg Thr Phe Lys Thr Leu Val Lys Tyr Leu Lys Thr
740                 745                 750                 755

ttc tat caa ttg aat ttg gag ggg ttt ctc ttg gac tgt tct ttt ggg   2362
Phe Tyr Gln Leu Asn Leu Glu Gly Phe Leu Leu Asp Cys Ser Phe Gly
                760                 765                 770

gta ttg gaa aac gtg ctt gaa aat atg gga tcc ctc ctt agg ttg gtt   2410
Val Leu Glu Asn Val Leu Glu Asn Met Gly Ser Leu Leu Arg Leu Val
            775                 780                 785

ttg agg gaa ttc aaa aca aag ttt acc tcc att gtc aaa tat gat aca   2458
Leu Arg Glu Phe Lys Thr Lys Phe Thr Ser Ile Val Lys Tyr Asp Thr
        790                 795                 800

ttt cat tgt tac aaa ttt atc aaa ttt cta tat gac ata agt aat tac   2506
Phe His Cys Tyr Lys Phe Ile Lys Phe Leu Tyr Asp Ile Ser Asn Tyr
    805                 810                 815

aca atc gtt aaa tat gtt gaa aca aac agc gac tgg gaa ggt gca cct   2554
Thr Ile Val Lys Tyr Val Glu Thr Asn Ser Asp Trp Glu Gly Ala Pro
820                 825                 830                 835

gaa cta ttg aat tgc att aaa cag ata att gtc aag gag ttt tcc tct   2602
Glu Leu Leu Asn Cys Ile Lys Gln Ile Ile Val Lys Glu Phe Ser Ser
                840                 845                 850

ttt gag agt tac ctg gaa ata gtc gag tgg gta caa aca ttg aat ata   2650
Phe Glu Ser Tyr Leu Glu Ile Val Glu Trp Val Gln Thr Leu Asn Ile
            855                 860                 865

taaatacact gctcatatac ccccaaacga gctttttaaa ttctcgatat ctctcaattg 2710

tcgc                                                              2714


<210> 2
<211> 867
<212> PRT
<213> Candida albicans

<400> 2
Met Thr Val Lys Val Asn Glu Lys Lys Thr Leu Leu Gln Tyr Val Leu
  1               5                  10                  15

Asp Asn Thr Ser Asn Asp Val Pro Leu Leu Pro Ser Leu Lys Glu Tyr
             20                  25                  30

Met Glu Thr Val Leu Val Tyr Lys Ser Ile Lys Arg Pro Leu Pro Ala
         35                  40                  45

Ile Arg Pro Gln Glu Ser Phe Asp Glu Phe Met Lys Glu Leu Val Thr
```

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     50                  55                  60

Arg Leu Val Met Glu Lys Ser Asn Asn Val Ile Ala Tyr Gly Tyr Lys
 65                  70                  75                  80

Thr Ser Ala Met Glu Ser Arg Ser Ile Phe Thr Thr Phe His Ser Ser
                 85                  90                  95

Gly Asn Phe Ile Leu Thr His Ile Thr Ser His Asn Trp Ser Thr Ile
            100                 105                 110

Phe Leu Leu Leu Gly Pro Lys Lys Phe Leu Glu Leu Leu Val Asn Asn
        115                 120                 125

Lys Gly Phe Val Ser Lys Val Asn Gly Glu Ser Val Gln Ile Phe Gly
    130                 135                 140

Asp Val Asn Ser His Arg Lys Ala Val Val Val Ser Lys Tyr Ile Thr
145                 150                 155                 160

Lys Phe Asn Val Leu Tyr Asn Ser Tyr Ser Arg Asp Phe Ser Arg Phe
                165                 170                 175

Glu Met Ile Arg Pro Ser Ile Gln Thr Ile Leu Gln Asp Ile Leu Ser
            180                 185                 190

Phe Ser Gly Leu Asn Pro Gly Arg Ser Ser Lys Arg Tyr Arg Gly Phe
        195                 200                 205

Lys Ser Leu Leu Ser Arg Ile Ile Ala Asn Asp Lys Lys Cys Arg Tyr
    210                 215                 220

Asp Ile Leu Tyr Ala Lys Phe Ile Gly Thr Ser Lys Cys Asn Phe Ala
225                 230                 235                 240

Asn Val Val Ser Asn Lys Thr Glu Ile Ser Gln Val Ile Gln Phe Val
                245                 250                 255

Leu Leu Val Leu Gly Lys Leu Leu Pro Leu Asp Ala Trp Gly Gly Val
            260                 265                 270

Ser Asn Lys Lys Ile Ile Lys Asp Arg Val Val Asp Phe Leu Leu Leu
        275                 280                 285

Gly Ala Asn Glu Lys Ile His Met Asp Asp Leu Phe Arg Gly Ile Arg
    290                 295                 300

Leu Lys Asp Phe Lys Trp Leu Gly Arg Ala His Gln Ile Ser Ser Lys
305                 310                 315                 320

Gln Asp Phe Glu Leu Arg Thr Ala Phe Leu Lys Gly Tyr Leu Trp Trp
                325                 330                 335

Leu Phe Glu His Leu Leu Lys Asn Ile Leu Arg Ser Phe Trp Tyr Ile
            340                 345                 350
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Thr Glu Thr Ser Ser Ile Val Ser Ser Glu Leu Asn Tyr Phe Pro Gln
        355                 360                 365

Tyr Leu Trp Lys Glu Leu Tyr Glu Ser Trp Val Ser Lys Tyr Ala Lys
    370                 375                 380

Asn Asn Leu Val Lys Met Pro Ser Lys Ile Gln Arg Glu Gln Leu Pro
385                 390                 395                 400

Cys Gly Lys Ile Lys Leu Ile Pro Lys Arg Ser Ser Phe Arg Val Ile
                405                 410                 415

Cys Val Pro Ile Lys Arg Ser Leu Lys Leu Leu Asn Lys Lys Leu Glu
            420                 425                 430

Leu Asp Thr Leu Glu Lys Glu Lys Arg Glu Phe Glu Arg Tyr Arg Lys
        435                 440                 445

Glu Val Leu Leu Pro Val Gly Gln Ile Leu Arg Leu Lys Leu Ser Lys
    450                 455                 460

Leu Arg Asp Thr Tyr Glu Ser Tyr Arg Ala Ser Val His Ser Ser Ser
465                 470                 475                 480

Asp Val Ala Glu Lys Ile Leu Asp Tyr Arg Asp Ser Leu Leu Thr Arg
                485                 490                 495

Phe Gly Glu Ile Pro Lys Leu Phe Ile Leu Lys Phe Asp Met Lys Glu
            500                 505                 510

Cys Tyr Asp Arg Leu Ser Gln Pro Val Leu Met Lys Lys Leu Glu Glu
        515                 520                 525

Leu Phe Glu Asn Gln Asp Asn Lys Thr Leu Tyr Tyr Val Arg Tyr Tyr
    530                 535                 540

Ala Gln Leu Asp Ala Ser His Lys Leu Lys Lys Val Lys Thr Thr Ile
545                 550                 555                 560

Asp Thr Gln Tyr His Asn Leu Asn Ile Leu Ser Ser Ser Arg His Leu
                565                 570                 575

Ser Asn Cys Lys Ser Leu Val Asp Lys Thr Lys Thr Ile Ala Leu Gln
            580                 585                 590

Lys Gly Asn Ile Leu Glu Val Cys Arg Ser Gln Ile Tyr Asp Val Val
        595                 600                 605

Gly Ser Val Lys Asp Ala Arg Gly Asn Leu His Leu Tyr Lys Arg Lys
    610                 615                 620

Arg Gly Val Phe Gln Gly Phe Ser Leu Leu Ser Ile Phe Cys Asp Ile
625                 630                 635                 640

Leu Tyr Ser Ala Met Val His Asp Cys Phe Gln Phe Leu Trp Lys Ser
                645                 650                 655
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Lys Gln Asp Phe Leu Phe Val Arg Leu Val Asp Asp Phe Leu Leu Val
            660                 665                 670

Thr Pro Asp Ser Asn Ile Tyr Asp Gln Val His Asn Ile Leu Ser Gly
        675                 680                 685

Lys Ile Leu Glu Ser Tyr Gly Ala Phe Val Asn Lys Asp Lys Thr Val
    690                 695                 700

Val Val Asn Gln Thr Thr Thr Lys Thr Ser Ile Asp Phe Val Gly Leu
705                 710                 715                 720

Glu Val Asn Thr Thr Asp Leu Ser Ile Lys Arg Asn Ser Gly Leu Ile
                725                 730                 735

Ser Leu Val Thr Thr Asn Phe Arg Thr Phe Lys Thr Leu Val Lys Tyr
            740                 745                 750

Leu Lys Thr Phe Tyr Gln Leu Asn Leu Glu Gly Phe Leu Leu Asp Cys
        755                 760                 765

Ser Phe Gly Val Leu Glu Asn Val Leu Glu Asn Met Gly Ser Leu Leu
    770                 775                 780

Arg Leu Val Leu Arg Glu Phe Lys Thr Lys Phe Thr Ser Ile Val Lys
785                 790                 795                 800

Tyr Asp Thr Phe His Cys Tyr Lys Phe Ile Lys Phe Leu Tyr Asp Ile
                805                 810                 815

Ser Asn Tyr Thr Ile Val Lys Tyr Val Glu Thr Asn Ser Asp Trp Glu
            820                 825                 830

Gly Ala Pro Glu Leu Leu Asn Cys Ile Lys Gln Ile Ile Val Lys Glu
        835                 840                 845

Phe Ser Ser Phe Glu Ser Tyr Leu Glu Ile Val Glu Trp Val Gln Thr
    850                 855                 860

Leu Asn Ile
865
```

<210> 3
<211> 2714
<212> DNA
<213> Candida albicans

<220>
<221> CDS
<222> (50)..(2650)
<223> TERT gene, strain 3153(A)

<220>
<221> misc_difference

<222> (389)..(2617)
<223> Amino acids at positions 114, 452, 487, 538, 634, 735 and 856 are translated as Ser in C. albicans, not as Leu (from ctg codons).

<400> 3

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cgttgttatt cacgcgtatc gtgagatatc atttcaaaga accacatac atg acc gtc 58
                                                      Met Thr Val
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aaa gta aat gag aag aag act tta ctt cag tat gtt cta gat aat aca 106
Lys Val Asn Glu Lys Lys Thr Leu Leu Gln Tyr Val Leu Asp Asn Thr
  5                  10                  15

agc aat gaa gtg cca ttg cta cct agt ttg aaa gag tac atg gag acg 154
Ser Asn Glu Val Pro Leu Leu Pro Ser Leu Lys Glu Tyr Met Glu Thr
 20                  25                  30                  35

gtg ctt gta tac caa tcc ata aaa cgg cct cta cca gcg att cga cca 202
Val Leu Val Tyr Gln Ser Ile Lys Arg Pro Leu Pro Ala Ile Arg Pro
                 40                  45                  50

caa gaa tca ttt gac gaa ttt atg aaa gag ttg gtg acc cgt tta gtt 250
Gln Glu Ser Phe Asp Glu Phe Met Lys Glu Leu Val Thr Arg Leu Val
             55                  60                  65

atg gaa aaa tcg aat aat gtt ata gct tat ggg tat aag acc tcc gca 298
Met Glu Lys Ser Asn Asn Val Ile Ala Tyr Gly Tyr Lys Thr Ser Ala
         70                  75                  80

atg gag agt cga agt ata ttt aca acg ttt cat tcg agt ggg aat ttt 346
Met Glu Ser Arg Ser Ile Phe Thr Thr Phe His Ser Ser Gly Asn Phe
     85                  90                  95

att tta act cac att aca agc cat aac tgg agt aca ata ttt ctg tta 394
Ile Leu Thr His Ile Thr Ser His Asn Trp Ser Thr Ile Phe Leu Leu
100                 105                 110                 115

ctc gga cct aaa aaa ttt cta gag cta tta gtt aat aat aag ggg ttt 442
Leu Gly Pro Lys Lys Phe Leu Glu Leu Leu Val Asn Asn Lys Gly Phe
                120                 125                 130

gtt agt aag gtg aat ggt gaa tct gtg caa ata ttc ggt gac gtg aac 490
Val Ser Lys Val Asn Gly Glu Ser Val Gln Ile Phe Gly Asp Val Asn
            135                 140                 145

tct cac aga aag gct gtc gtc gtt tcc aaa tac att acc aaa ttc aat 538
Ser His Arg Lys Ala Val Val Val Ser Lys Tyr Ile Thr Lys Phe Asn
        150                 155                 160

gtg ctt tac aac tcc tat tcc agg gac ttc tca cgc ttt gag atg ata 586
Val Leu Tyr Asn Ser Tyr Ser Arg Asp Phe Ser Arg Phe Glu Met Ile
    165                 170                 175

aga ccc agt att caa act ata tta cag gat att ctt tcc ttt tct ggt 634
Arg Pro Ser Ile Gln Thr Ile Leu Gln Asp Ile Leu Ser Phe Ser Gly
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180                 185                 190                 195

ttg aat cct gga aga tca tcc aaa aga tat cga ggc ttc aaa agt ttg   682
Leu Asn Pro Gly Arg Ser Ser Lys Arg Tyr Arg Gly Phe Lys Ser Leu
                200                 205                 210

ctc tcg aga att att gct aat gat aag aaa tgt aga tac gac att cta   730
Leu Ser Arg Ile Ile Ala Asn Asp Lys Lys Cys Arg Tyr Asp Ile Leu
            215                 220                 225

tat gct aag ttt att ggt acg tca aaa tgc aat ttt gct aat gtg gtg   778
Tyr Ala Lys Phe Ile Gly Thr Ser Lys Cys Asn Phe Ala Asn Val Val
        230                 235                 240

agt aat aag aca gaa ata tcc cag gta att caa ttt gta ctt tta gta   826
Ser Asn Lys Thr Glu Ile Ser Gln Val Ile Gln Phe Val Leu Leu Val
    245                 250                 255

ttg ggt aaa ttg tta cct ttg gat gct tgg gga ggt gtt tcc aat aaa   874
Leu Gly Lys Leu Leu Pro Leu Asp Ala Trp Gly Gly Val Ser Asn Lys
260                 265                 270                 275

aag att att aag gac cga gtg gta gat ttt ttg tta ctt ggg gca aat   922
Lys Ile Ile Lys Asp Arg Val Val Asp Phe Leu Leu Leu Gly Ala Asn
                280                 285                 290

gaa aag ata cat atg gat gat tta ttt aga gga att aga cta aaa gat   970
Glu Lys Ile His Met Asp Asp Leu Phe Arg Gly Ile Arg Leu Lys Asp
            295                 300                 305

ttc aag tgg ttg ggc aga gct cac caa att tct tcg aaa caa gat ttc   1018
Phe Lys Trp Leu Gly Arg Ala His Gln Ile Ser Ser Lys Gln Asp Phe
        310                 315                 320

gag ctc cga aca gct ttt cta aaa ggg tat cta tgg tgg ttg ttt gaa   1066
Glu Leu Arg Thr Ala Phe Leu Lys Gly Tyr Leu Trp Trp Leu Phe Glu
    325                 330                 335

cat tta ctt aaa aat att ctc cgt tct ttc tgg tac att act gaa act   1114
His Leu Leu Lys Asn Ile Leu Arg Ser Phe Trp Tyr Ile Thr Glu Thr
340                 345                 350                 355

tca agt ata gtg agt tta gag ttg aat tat ttt cct cag tat tta tgg   1162
Ser Ser Ile Val Ser Leu Glu Leu Asn Tyr Phe Pro Gln Tyr Leu Trp
                360                 365                 370

aaa gag cta tac gag tca tgg gtg tct aaa tat gca aag aat aat ctt   1210
Lys Glu Leu Tyr Glu Ser Trp Val Ser Lys Tyr Ala Lys Asn Asn Leu
            375                 380                 385

gtg aaa atg cca tca aag atc caa aga gaa caa cta cca tgt ggg aaa   1258
Val Lys Met Pro Ser Lys Ile Gln Arg Glu Gln Leu Pro Cys Gly Lys
        390                 395                 400

att aaa ctc ata ccc aag cgc tcg agc ttt cgt gtt att tgt gta cct   1306
Ile Lys Leu Ile Pro Lys Arg Ser Ser Phe Arg Val Ile Cys Val Pro
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    405                 410                 415

ata aaa cga tcc ttg aaa cta ttg aac aaa aaa ttg gaa ttg gac aca   1354
Ile Lys Arg Ser Leu Lys Leu Leu Asn Lys Lys Leu Glu Leu Asp Thr
420                 425                 430                 435

ttg gaa aag gag aaa agg gaa ttt gaa agg tac aga aaa gag gtt tta   1402
Leu Glu Lys Glu Lys Arg Glu Phe Glu Arg Tyr Arg Lys Glu Val Leu
                440                 445                 450

ctg cca gtg gga caa ata cta cgc ttg aaa tta tcg aaa cta aga gat   1450
Leu Pro Val Gly Gln Ile Leu Arg Leu Lys Leu Ser Lys Leu Arg Asp
            455                 460                 465

aca tat gaa agc tat agg gct tca gta cat tcc agt tct gat gtg gct   1498
Thr Tyr Glu Ser Tyr Arg Ala Ser Val His Ser Ser Ser Asp Val Ala
        470                 475                 480

gaa aag ata ctg gat tat aga gac tcc ttg tta acc aga ttt ggc gaa   1546
Glu Lys Ile Leu Asp Tyr Arg Asp Ser Leu Leu Thr Arg Phe Gly Glu
    485                 490                 495

atc cct aag ctt ttc atc tta aag ttt gac atg aaa gaa tgt tat gat   1594
Ile Pro Lys Leu Phe Ile Leu Lys Phe Asp Met Lys Glu Cys Tyr Asp
500                 505                 510                 515

aga ctc agc caa cct gta tta atg aaa aaa cta gag gaa ctt ttc gaa   1642
Arg Leu Ser Gln Pro Val Leu Met Lys Lys Leu Glu Glu Leu Phe Glu
                520                 525                 530

aac caa gat aat aag act ctg tat tat gtt cga tac tac gct cag ttg   1690
Asn Gln Asp Asn Lys Thr Leu Tyr Tyr Val Arg Tyr Tyr Ala Gln Leu
            535                 540                 545

gac gcg tca cat aaa ttg aaa aaa gtg aaa acc act ata gat acc cag   1738
Asp Ala Ser His Lys Leu Lys Lys Val Lys Thr Thr Ile Asp Thr Gln
        550                 555                 560

tat cac aat tta aac att ttg tcg agc tca agg cat ctc agt aat tgt   1786
Tyr His Asn Leu Asn Ile Leu Ser Ser Ser Arg His Leu Ser Asn Cys
    565                 570                 575

aaa tct ttg gtc gat aag acc aag aca ata gcg ttg caa aaa ggt aac   1834
Lys Ser Leu Val Asp Lys Thr Lys Thr Ile Ala Leu Gln Lys Gly Asn
580                 585                 590                 595

att ttg gaa gtt tgt cga agc caa atc tac gat gtt gtt ggt tca gtt   1882
Ile Leu Glu Val Cys Arg Ser Gln Ile Tyr Asp Val Val Gly Ser Val
                600                 605                 610

aaa gat gca cga ggg aat tta cac cta tat aaa agg aag agg ggc gtg   1930
Lys Asp Ala Arg Gly Asn Leu His Leu Tyr Lys Arg Lys Arg Gly Val
            615                 620                 625

ttt cag gga ttc tca ttg ctg tct ata ttt tgt gac atc cta tat agt   1978
Phe Gln Gly Phe Ser Leu Leu Ser Ile Phe Cys Asp Ile Leu Tyr Ser
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         630                 635                 640

gca atg gtt cat gat tgt ttt caa ttc tta tgg aag tcg aaa cag gat   2026
Ala Met Val His Asp Cys Phe Gln Phe Leu Trp Lys Ser Lys Gln Asp
    645                 650                 655

ttt tta ttt gta cga ttg gta gat gac ttt tta ctt gta acg ccc gat   2074
Phe Leu Phe Val Arg Leu Val Asp Asp Phe Leu Leu Val Thr Pro Asp
660                 665                 670                 675

tcg aat att tat gat caa gtg cac aat ata tta tca gga aaa ata ctt   2122
Ser Asn Ile Tyr Asp Gln Val His Asn Ile Leu Ser Gly Lys Ile Leu
                680                 685                 690

gag agc tat gga gct ttt gtt aat aaa gat aaa aca gtc gtt gtt aat   2170
Glu Ser Tyr Gly Ala Phe Val Asn Lys Asp Lys Thr Val Val Val Asn
            695                 700                 705

caa aca acc acg aaa cca agt ata gat ttc gtt ggg ctc gaa gtg aat   2218
Gln Thr Thr Thr Lys Pro Ser Ile Asp Phe Val Gly Leu Glu Val Asn
        710                 715                 720

aca aca gat cta agc atc aaa agg aac tcc ggt ctg ata agt ttg gtt   2266
Thr Thr Asp Leu Ser Ile Lys Arg Asn Ser Gly Leu Ile Ser Leu Val
    725                 730                 735

acg aca aac ttc aga aca ttc aag act tta gtt aag tat tta aag act   2314
Thr Thr Asn Phe Arg Thr Phe Lys Thr Leu Val Lys Tyr Leu Lys Thr
740                 745                 750                 755

ttc tat caa ttg aat ttg gag ggg ttt ctc ttg gac tgt tct ttt ggg   2362
Phe Tyr Gln Leu Asn Leu Glu Gly Phe Leu Leu Asp Cys Ser Phe Gly
                760                 765                 770

gta ttg gaa aac gtg ctt gaa aat atg gga tcc ctc ctt agg ttg gtt   2410
Val Leu Glu Asn Val Leu Glu Asn Met Gly Ser Leu Leu Arg Leu Val
            775                 780                 785

ttg agg gaa ttc aaa aca aag ttt acc tcc att gtc aaa tat gat aca   2458
Leu Arg Glu Phe Lys Thr Lys Phe Thr Ser Ile Val Lys Tyr Asp Thr
        790                 795                 800

ttt cat tgt tac aaa ttt atc aaa ttt cta tat gac ata agt aat tac   2506
Phe His Cys Tyr Lys Phe Ile Lys Phe Leu Tyr Asp Ile Ser Asn Tyr
    805                 810                 815

aca atc gtt aaa tat gtt gaa aca aac agc gac tgg gat ggt gca cct   2554
Thr Ile Val Lys Tyr Val Glu Thr Asn Ser Asp Trp Asp Gly Ala Pro
820                 825                 830                 835

gaa cta ttg aat tgc att aaa cag ata att gtc aag gag ttt tcc tct   2602
Glu Leu Leu Asn Cys Ile Lys Gln Ile Ile Val Lys Glu Phe Ser Ser
                840                 845                 850

ttt gag agt tac ctg gaa ata gtc gag tgg gta caa aca ttg aat ata   2650
Phe Glu Ser Tyr Leu Glu Ile Val Glu Trp Val Gln Thr Leu Asn Ile
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855 860 865

taaatacact gctcatatac ccccaaacga gctttttaaa ttctcgatat ctctcaattg 2710

tcgc 2714

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<212> PRT
<213> Candida albicans

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Met Thr Val Lys Val Asn Glu Lys Lys Thr Leu Leu Gln Tyr Val Leu
  1               5                  10                  15

Asp Asn Thr Ser Asn Glu Val Pro Leu Leu Pro Ser Leu Lys Glu Tyr
             20                  25                  30

Met Glu Thr Val Leu Val Tyr Gln Ser Ile Lys Arg Pro Leu Pro Ala
         35                  40                  45

Ile Arg Pro Gln Glu Ser Phe Asp Glu Phe Met Lys Glu Leu Val Thr
     50                  55                  60

Arg Leu Val Met Glu Lys Ser Asn Asn Val Ile Ala Tyr Gly Tyr Lys
 65                  70                  75                  80

Thr Ser Ala Met Glu Ser Arg Ser Ile Phe Thr Thr Phe His Ser Ser
                 85                  90                  95

Gly Asn Phe Ile Leu Thr His Ile Thr Ser His Asn Trp Ser Thr Ile
            100                 105                 110

Phe Leu Leu Leu Gly Pro Lys Lys Phe Leu Glu Leu Leu Val Asn Asn
        115                 120                 125

Lys Gly Phe Val Ser Lys Val Asn Gly Glu Ser Val Gln Ile Phe Gly
    130                 135                 140

Asp Val Asn Ser His Arg Lys Ala Val Val Val Ser Lys Tyr Ile Thr
145                 150                 155                 160

Lys Phe Asn Val Leu Tyr Asn Ser Tyr Ser Arg Asp Phe Ser Arg Phe
                165                 170                 175

Glu Met Ile Arg Pro Ser Ile Gln Thr Ile Leu Gln Asp Ile Leu Ser
            180                 185                 190

Phe Ser Gly Leu Asn Pro Gly Arg Ser Ser Lys Arg Tyr Arg Gly Phe
        195                 200                 205

Lys Ser Leu Leu Ser Arg Ile Ile Ala Asn Asp Lys Lys Cys Arg Tyr
    210                 215                 220

Asp Ile Leu Tyr Ala Lys Phe Ile Gly Thr Ser Lys Cys Asn Phe Ala
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225 230 235 240

Asn Val Val Ser Asn Lys Thr Glu Ile Ser Gln Val Ile Gln Phe Val
245 250 255

Leu Leu Val Leu Gly Lys Leu Leu Pro Leu Asp Ala Trp Gly Gly Val
260 265 270

Ser Asn Lys Lys Ile Ile Lys Asp Arg Val Val Asp Phe Leu Leu Leu
275 280 285

Gly Ala Asn Glu Lys Ile His Met Asp Asp Leu Phe Arg Gly Ile Arg
290 295 300

Leu Lys Asp Phe Lys Trp Leu Gly Arg Ala His Gln Ile Ser Ser Lys
305 310 315 320

Gln Asp Phe Glu Leu Arg Thr Ala Phe Leu Lys Gly Tyr Leu Trp Trp
325 330 335

Leu Phe Glu His Leu Leu Lys Asn Ile Leu Arg Ser Phe Trp Tyr Ile
340 345 350

Thr Glu Thr Ser Ser Ile Val Ser Leu Glu Leu Asn Tyr Phe Pro Gln
355 360 365

Tyr Leu Trp Lys Glu Leu Tyr Glu Ser Trp Val Ser Lys Tyr Ala Lys
370 375 380

Asn Asn Leu Val Lys Met Pro Ser Lys Ile Gln Arg Glu Gln Leu Pro
385 390 395 400

Cys Gly Lys Ile Lys Leu Ile Pro Lys Arg Ser Ser Phe Arg Val Ile
405 410 415

Cys Val Pro Ile Lys Arg Ser Leu Lys Leu Leu Asn Lys Lys Leu Glu
420 425 430

Leu Asp Thr Leu Glu Lys Glu Lys Arg Glu Phe Glu Arg Tyr Arg Lys
435 440 445

Glu Val Leu Leu Pro Val Gly Gln Ile Leu Arg Leu Lys Leu Ser Lys
450 455 460

Leu Arg Asp Thr Tyr Glu Ser Tyr Arg Ala Ser Val His Ser Ser Ser
465 470 475 480

Asp Val Ala Glu Lys Ile Leu Asp Tyr Arg Asp Ser Leu Leu Thr Arg
485 490 495

Phe Gly Glu Ile Pro Lys Leu Phe Ile Leu Lys Phe Asp Met Lys Glu
500 505 510

Cys Tyr Asp Arg Leu Ser Gln Pro Val Leu Met Lys Lys Leu Glu Glu
515 520 525

```
Leu Phe Glu Asn Gln Asp Asn Lys Thr Leu Tyr Tyr Val Arg Tyr Tyr
    530                 535                 540

Ala Gln Leu Asp Ala Ser His Lys Leu Lys Lys Val Lys Thr Thr Ile
545                 550                 555                 560

Asp Thr Gln Tyr His Asn Leu Asn Ile Leu Ser Ser Ser Arg His Leu
                565                 570                 575

Ser Asn Cys Lys Ser Leu Val Asp Lys Thr Lys Thr Ile Ala Leu Gln
            580                 585                 590

Lys Gly Asn Ile Leu Glu Val Cys Arg Ser Gln Ile Tyr Asp Val Val
        595                 600                 605

Gly Ser Val Lys Asp Ala Arg Gly Asn Leu His Leu Tyr Lys Arg Lys
    610                 615                 620

Arg Gly Val Phe Gln Gly Phe Ser Leu Leu Ser Ile Phe Cys Asp Ile
625                 630                 635                 640

Leu Tyr Ser Ala Met Val His Asp Cys Phe Gln Phe Leu Trp Lys Ser
                645                 650                 655

Lys Gln Asp Phe Leu Phe Val Arg Leu Val Asp Asp Phe Leu Leu Val
            660                 665                 670

Thr Pro Asp Ser Asn Ile Tyr Asp Gln Val His Asn Ile Leu Ser Gly
        675                 680                 685

Lys Ile Leu Glu Ser Tyr Gly Ala Phe Val Asn Lys Asp Lys Thr Val
    690                 695                 700

Val Val Asn Gln Thr Thr Thr Lys Pro Ser Ile Asp Phe Val Gly Leu
705                 710                 715                 720

Glu Val Asn Thr Thr Asp Leu Ser Ile Lys Arg Asn Ser Gly Leu Ile
                725                 730                 735

Ser Leu Val Thr Thr Asn Phe Arg Thr Phe Lys Thr Leu Val Lys Tyr
            740                 745                 750

Leu Lys Thr Phe Tyr Gln Leu Asn Leu Glu Gly Phe Leu Leu Asp Cys
        755                 760                 765

Ser Phe Gly Val Leu Glu Asn Val Leu Glu Asn Met Gly Ser Leu Leu
    770                 775                 780

Arg Leu Val Leu Arg Glu Phe Lys Thr Lys Phe Thr Ser Ile Val Lys
785                 790                 795                 800

Tyr Asp Thr Phe His Cys Tyr Lys Phe Ile Lys Phe Leu Tyr Asp Ile
                805                 810                 815

Ser Asn Tyr Thr Ile Val Lys Tyr Val Glu Thr Asn Ser Asp Trp Asp
            820                 825                 830
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Gly Ala Pro Glu Leu Leu Asn Cys Ile Lys Gln Ile Ile Val Lys Glu
835 840 845

Phe Ser Ser Phe Glu Ser Tyr Leu Glu Ile Val Glu Trp Val Gln Thr
850 855 860

Leu Asn Ile
865

<210> 5
<211> 10640
<212> DNA
<213> Plasmodium falciparum

<220>
<221> CDS
<222> (834)..(7385)
<223> TERT gene

<220>
<221> unsure
<222> (1821)..(1837)
<223> m at position 1821 = a or c; w at position 1837 = a or t. Xaa (amino acid) at position 330 = Leu or Ile; Xaa at position 335 = Asp or Gly.

<400> 5
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atttaataaa tgaaataata atagatacat catttttaa agagaattat gattttcaat 120

atttttaga aaatgtttta ttattagaag atttagtttt aaaaaagttg gataataaat 180

taaatgatga ggattttata tttaaagaaa ataaaaaagt atctataaat aattggaaag 240

aatgttatag tcatattaag aaaaaattaa atatcaaagg tatggatgaa aaaagtaaga 300

tatataataa ttctatttta ttatttaatt ctactaaatt ttcctatgat gatataaatt 360

gttgtgattc tttttatggt ttacaagtat gggatatatt atttaattat gtatcattcg 420

atttttaaa ttatttattg tctaatacac ttatatttat atctgactac ttttttatca 480

atacaaataa taattttaaa acatatgtaa agtcatctta ctttattaaa attgcagaaa 540

tacaattaaa ttatcaagat gctcaaaata tagaaagaaa tatttttca aaaaaaaaaa 600

atttatatta taaaaataca aaactagtaa aattaacata tcaaaaaaaa agcatcaagg 660

atagtacaac accaaattta accatccaga aaaaagctag atagggaaag gaaaaaaaat 720

tcagtaaaaa tataagtacg aatgaacata tagatataaa tataaataat tatatatata 780

atacattaaa tcaaaacaat gaagtcaatc aatataatgt taatcatctc aat atg 836

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                                                                  Met
                                                                   1

gat aaa aat att acc tac aaa gaa aag gag tcg cag aat tat acc atc    884
Asp Lys Asn Ile Thr Tyr Lys Glu Lys Glu Ser Gln Asn Tyr Thr Ile
               5                  10                  15

aat aat aat tta tta aat gat caa ctt tta tat tat aat aaa aca tat    932
Asn Asn Asn Leu Leu Asn Asp Gln Leu Leu Tyr Tyr Asn Lys Thr Tyr
          20                  25                  30

cag aat aat gta aat aca cat att tat tca aat gat aat aaa acg cct    980
Gln Asn Asn Val Asn Thr His Ile Tyr Ser Asn Asp Asn Lys Thr Pro
      35                  40                  45

att att gct aac cag tgt ata gat ata cat aac cgt gta agt gat ccg   1028
Ile Ile Ala Asn Gln Cys Ile Asp Ile His Asn Arg Val Ser Asp Pro
 50                  55                  60                  65

aca agg aaa aat ata ttt tat cat agt ata aac agc ctt tcg tat gaa   1076
Thr Arg Lys Asn Ile Phe Tyr His Ser Ile Asn Ser Leu Ser Tyr Glu
                 70                  75                  80

gca agt ttg aat att ttt cat tat aat aat ctg aca caa cat aca aca   1124
Ala Ser Leu Asn Ile Phe His Tyr Asn Asn Leu Thr Gln His Thr Thr
               85                  90                  95

tat ata gat aca cca aat aaa agt caa aca tgt ata aat agt cct atg   1172
Tyr Ile Asp Thr Pro Asn Lys Ser Gln Thr Cys Ile Asn Ser Pro Met
          100                 105                 110

caa cat gaa ata gat gaa cat tca aat aat gaa ttg aaa aat caa aaa   1220
Gln His Glu Ile Asp Glu His Ser Asn Asn Glu Leu Lys Asn Gln Lys
      115                 120                 125

tgt act caa tat gaa tat gta gat aac gta tgc aca acg aat aaa aat   1268
Cys Thr Gln Tyr Glu Tyr Val Asp Asn Val Cys Thr Thr Asn Lys Asn
130                 135                 140                 145

ata tca aac gat aat ata agt gat aaa tgt att act act aaa aat ata   1316
Ile Ser Asn Asp Asn Ile Ser Asp Lys Cys Ile Thr Thr Lys Asn Ile
                150                 155                 160

cct cta aaa tat cat att aat aaa aaa tat aaa tac tta tta aaa aaa   1364
Pro Leu Lys Tyr His Ile Asn Lys Lys Tyr Lys Tyr Leu Leu Lys Lys
               165                 170                 175

aaa tac cat aca atg tac aca aat aat gat cat tca tat gga aag tat   1412
Lys Tyr His Thr Met Tyr Thr Asn Asn Asp His Ser Tyr Gly Lys Tyr
          180                 185                 190

ttg tat ctt gtt cag tgc agt ggt cga att tta aaa aat gac ttt ttt   1460
Leu Tyr Leu Val Gln Cys Ser Gly Arg Ile Leu Lys Asn Asp Phe Phe
      195                 200                 205

aag gac atg aaa caa ata caa gaa gaa aga aag aaa tat aca tca aat   1508
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Lys Asp Met Lys Gln Ile Gln Glu Glu Arg Lys Lys Tyr Thr Ser Asn
210                 215                 220                 225

att aag atc aac agt gaa tat acc aat aat ata ata att aac aac aac   1556
Ile Lys Ile Asn Ser Glu Tyr Thr Asn Asn Ile Ile Ile Asn Asn Asn
                230                 235                 240

aac aac aac aac aat aat aat aat aat aat aac aat aat gtg cat ggt   1604
Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Val His Gly
            245                 250                 255

ttt gga cat ata aac aat ttg ttc tct tct aac gaa ttt cca tct tct   1652
Phe Gly His Ile Asn Asn Leu Phe Ser Ser Asn Glu Phe Pro Ser Ser
        260                 265                 270

aac att tca agc tgt act aat tac aca gaa aaa aat gat aaa tta aca   1700
Asn Ile Ser Ser Cys Thr Asn Tyr Thr Glu Lys Asn Asp Lys Leu Thr
    275                 280                 285

cac ata agg gaa act tcc tta cta ata aca gaa aat tct tca aaa aaa   1748
His Ile Arg Glu Thr Ser Leu Leu Ile Thr Glu Asn Ser Ser Lys Lys
290                 295                 300                 305

gat aag ctg tta cca gaa ata gat ttc ttt tct gag gat aga aag gag   1796
Asp Lys Leu Leu Pro Glu Ile Asp Phe Phe Ser Glu Asp Arg Lys Glu
                310                 315                 320

aaa tca tca tcg gtt ggt tat gac mta aaa aaa aag aat gwt agt aat   1844
Lys Ser Ser Ser Val Gly Tyr Asp Xaa Lys Lys Lys Asn Xaa Ser Asn
            325                 330                 335

att aaa aga ttt cat aat aaa ata aac aga acg aaa gaa gaa aaa aaa   1892
Ile Lys Arg Phe His Asn Lys Ile Asn Arg Thr Lys Glu Glu Lys Lys
        340                 345                 350

aaa aaa tgg aat aaa ata ata atc aat aga aac aac att tta caa cac   1940
Lys Lys Trp Asn Lys Ile Ile Ile Asn Arg Asn Asn Ile Leu Gln His
    355                 360                 365

aat aca act aat aaa tgt aaa acc ttt cta ttt aat aaa cac ata ata   1988
Asn Thr Thr Asn Lys Cys Lys Thr Phe Leu Phe Asn Lys His Ile Ile
370                 375                 380                 385

ttt gat aaa ata gaa aat aat aat att cct tta ttt att tat gat tta   2036
Phe Asp Lys Ile Glu Asn Asn Asn Ile Pro Leu Phe Ile Tyr Asp Leu
                390                 395                 400

tta aac tat ata ttt aaa tca gat caa aca tat ttt tat cat aat aat   2084
Leu Asn Tyr Ile Phe Lys Ser Asp Gln Thr Tyr Phe Tyr His Asn Asn
            405                 410                 415

ttt ata gat gaa tat aag cag aaa ata tgt aaa caa ata aaa tgt tca   2132
Phe Ile Asp Glu Tyr Lys Gln Lys Ile Cys Lys Gln Ile Lys Cys Ser
        420                 425                 430

acc aaa aaa aat gac ata tct cat ata att aca tcg agg aaa gaa aat   2180
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Thr Lys Lys Asn Asp Ile Ser His Ile Ile Thr Ser Arg Lys Glu Asn
    435                 440                 445

cat tta ttt cat gta caa aaa ctt gaa aat aat tat aaa cat cca aat   2228
His Leu Phe His Val Gln Lys Leu Glu Asn Asn Tyr Lys His Pro Asn
450                 455                 460                 465

ata aat aaa cag cta aga aag acg aaa atc ttg aaa tat gta tat aat   2276
Ile Asn Lys Gln Leu Arg Lys Thr Lys Ile Leu Lys Tyr Val Tyr Asn
                470                 475                 480

tat ttt aag gaa ttt att aat aat gta att aat aca aaa ttt ggt aaa   2324
Tyr Phe Lys Glu Phe Ile Asn Asn Val Ile Asn Thr Lys Phe Gly Lys
            485                 490                 495

ata tat agg aaa ttt ttt cct cga aaa cat ata tta aat aag ata cat   2372
Ile Tyr Arg Lys Phe Phe Pro Arg Lys His Ile Leu Asn Lys Ile His
        500                 505                 510

aaa ata ttt aaa att ata aga tta caa ata ata aaa aaa tat cgt att   2420
Lys Ile Phe Lys Ile Ile Arg Leu Gln Ile Ile Lys Lys Tyr Arg Ile
    515                 520                 525

ata aat ata cga atg aat cga aaa ttt att aaa caa aaa gta tat gat   2468
Ile Asn Ile Arg Met Asn Arg Lys Phe Ile Lys Gln Lys Val Tyr Asp
530                 535                 540                 545

aca ttt ttt aaa aat tat gat ttc tta tca ttt tca ttt aaa acg tat   2516
Thr Phe Phe Lys Asn Tyr Asp Phe Leu Ser Phe Ser Phe Lys Thr Tyr
                550                 555                 560

aag att att aat ttt atg gta tat ata acc aaa aaa tgt ata cct atc   2564
Lys Ile Ile Asn Phe Met Val Tyr Ile Thr Lys Lys Cys Ile Pro Ile
            565                 570                 575

aaa tta tta ggt agt aag cat aat ttc aaa ata ttt tta aaa aat gta   2612
Lys Leu Leu Gly Ser Lys His Asn Phe Lys Ile Phe Leu Lys Asn Val
        580                 585                 590

aaa aaa ttt ttg tta ttt aat tat aaa gaa agt ttt tcg tta aat caa   2660
Lys Lys Phe Leu Leu Phe Asn Tyr Lys Glu Ser Phe Ser Leu Asn Gln
    595                 600                 605

gta atg aaa aat att aag gta aaa aat ata ttt caa aaa aaa ata agt   2708
Val Met Lys Asn Ile Lys Val Lys Asn Ile Phe Gln Lys Lys Ile Ser
610                 615                 620                 625

aaa tat aat ata aaa aat aga att tta tta aag aat ata ttt gat aac   2756
Lys Tyr Asn Ile Lys Asn Arg Ile Leu Leu Lys Asn Ile Phe Asp Asn
                630                 635                 640

aac tat gaa aac aaa att tta cat aga aat aat aag gaa atc ata aca   2804
Asn Tyr Glu Asn Lys Ile Leu His Arg Asn Asn Lys Glu Ile Ile Thr
            645                 650                 655

aat ata aat gat aac ata aaa ata tat aat aaa aaa aat gat aat tta   2852
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Asn Ile Asn Asp Asn Ile Lys Ile Tyr Asn Lys Lys Asn Asp Asn Leu
        660                 665                 670

aat aat tca ttt aaa ata aaa aca acg tta ttc aat aaa ttg agg aga   2900
Asn Asn Ser Phe Lys Ile Lys Thr Thr Leu Phe Asn Lys Leu Arg Arg
    675                 680                 685

aaa tat ttc aat aaa att aaa aaa att aat ata gct ata caa aaa aga   2948
Lys Tyr Phe Asn Lys Ile Lys Lys Ile Asn Ile Ala Ile Gln Lys Arg
690                 695                 700                 705

cat ctt atg aat aga tta ata tat ttc ctt ttt aat tat ttt att atg   2996
His Leu Met Asn Arg Leu Ile Tyr Phe Leu Phe Asn Tyr Phe Ile Met
                710                 715                 720

cca cta att aga aga ttt ttt ttt cta acc aaa tct gag caa acc tta   3044
Pro Leu Ile Arg Arg Phe Phe Phe Leu Thr Lys Ser Glu Gln Thr Leu
            725                 730                 735

cat aaa aca att ttc ttt gat aga aaa att tgg aat cat ttt acg aaa   3092
His Lys Thr Ile Phe Phe Asp Arg Lys Ile Trp Asn His Phe Thr Lys
        740                 745                 750

att tcg aac ttt tgt ctt tac cat caa att ttt agg aat aaa aag tta   3140
Ile Ser Asn Phe Cys Leu Tyr His Gln Ile Phe Arg Asn Lys Lys Leu
    755                 760                 765

aaa aaa aga aat gaa ccc aaa atg gat tat gta caa aat atg ttc aat   3188
Lys Lys Arg Asn Glu Pro Lys Met Asp Tyr Val Gln Asn Met Phe Asn
770                 775                 780                 785

gtg aag aaa aaa ggt gaa aaa ata aaa aca aat aaa tat ata ttt att   3236
Val Lys Lys Lys Gly Glu Lys Ile Lys Thr Asn Lys Tyr Ile Phe Ile
                790                 795                 800

aag aaa atg aaa aaa aag agc act aat aaa tgt att aat aat aaa ttt   3284
Lys Lys Met Lys Lys Lys Ser Thr Asn Lys Cys Ile Asn Asn Lys Phe
            805                 810                 815

tcc aaa aaa tgt atc cct aaa aaa aaa aaa aaa aat tta tat aac atc   3332
Ser Lys Lys Cys Ile Pro Lys Lys Lys Lys Lys Asn Leu Tyr Asn Ile
        820                 825                 830

aca cgt cat aat aat ata ttt att aaa aag gat atg gaa aaa aaa tca   3380
Thr Arg His Asn Asn Ile Phe Ile Lys Lys Asp Met Glu Lys Lys Ser
    835                 840                 845

aaa act aac aat tta att aat aaa agt ata gat aat tta tac aaa tta   3428
Lys Thr Asn Asn Leu Ile Asn Lys Ser Ile Asp Asn Leu Tyr Lys Leu
850                 855                 860                 865

aag gaa att aac aaa aaa agt gtt aga cca tat att aaa aaa ttt tac   3476
Lys Glu Ile Asn Lys Lys Ser Val Arg Pro Tyr Ile Lys Lys Phe Tyr
                870                 875                 880

tat aaa ata aaa aag aaa tat ttt gct cta aaa aaa atg tat att cat   3524
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Tyr Lys Ile Lys Lys Lys Tyr Phe Ala Leu Lys Lys Met Tyr Ile His
            885                 890                 895

atg aga atg gca aaa gaa gaa aaa agt aac ata aaa tta gaa aga gca   3572
Met Arg Met Ala Lys Glu Glu Lys Ser Asn Ile Lys Leu Glu Arg Ala
        900                 905                 910

ttc aaa cat ttt ttt att ttt gct caa gaa aaa gaa cac ata ttg aaa   3620
Phe Lys His Phe Phe Ile Phe Ala Gln Glu Lys Glu His Ile Leu Lys
    915                 920                 925

tat ttt agt tcc cat ttt ttt caa aat aga aag ata aat tat ggt aaa   3668
Tyr Phe Ser Ser His Phe Phe Gln Asn Arg Lys Ile Asn Tyr Gly Lys
930                 935                 940                 945

cga ttt aat aaa cta ata cat cga ata aaa aat ata ata ata aag caa   3716
Arg Phe Asn Lys Leu Ile His Arg Ile Lys Asn Ile Ile Ile Lys Gln
                950                 955                 960

aac agt gga att gtt aaa aat aag gat aag aca ttt tta cat tta atc   3764
Asn Ser Gly Ile Val Lys Asn Lys Asp Lys Thr Phe Leu His Leu Ile
            965                 970                 975

aaa aat aaa agt aac aaa aat aac aat aac aag aag aag aac aaa aat   3812
Lys Asn Lys Ser Asn Lys Asn Asn Asn Asn Lys Lys Lys Asn Lys Asn
        980                 985                 990

aat tat aac aat aat aat att aat aat aac aat aat aat aat aac aat   3860
Asn Tyr Asn Asn Asn Asn Ile Asn Asn Asn Asn Asn Asn Asn Asn Asn
    995                1000                1005

aat aat att aat aat aat aat aac aac aaa tgt aaa cta tca aat tcc   3908
Asn Asn Ile Asn Asn Asn Asn Asn Asn Lys Cys Lys Leu Ser Asn Ser
1010                1015                1020                1025

aaa agg tat aat ata aga aat aat aat aat aat aaa aag gct aaa aat   3956
Lys Arg Tyr Asn Ile Arg Asn Asn Asn Asn Asn Lys Lys Ala Lys Asn
                1030                1035                1040

aat gag aag aac aat att gat gat tcc aat tta gaa aaa aaa aaa aaa   4004
Asn Glu Lys Asn Asn Ile Asp Asp Ser Asn Leu Glu Lys Lys Lys Lys
            1045                1050                1055

aaa ata tac ata tat aaa ata aaa aat att ata gag aaa aga aat ttt   4052
Lys Ile Tyr Ile Tyr Lys Ile Lys Asn Ile Ile Glu Lys Arg Asn Phe
        1060                1065                1070

atg tta aaa tta aat tca atc aat cat ttt ata tct aaa aag tta aga   4100
Met Leu Lys Leu Asn Ser Ile Asn His Phe Ile Ser Lys Lys Leu Arg
    1075                1080                1085

att aat tgg ata cca aaa aaa aaa gga tta aga cct tta att aat ttg   4148
Ile Asn Trp Ile Pro Lys Lys Lys Gly Leu Arg Pro Leu Ile Asn Leu
1090                1095                1100                1105

tct act tta aat gtg cca gaa att gtc aag caa cga att ttt gaa att   4196
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Ser Thr Leu Asn Val Pro Glu Ile Val Lys Gln Arg Ile Phe Glu Ile
                1110                1115                1120

ttg aaa agt aaa aaa agc agt gaa ttt tat ttc cat aat att ttg aat   4244
Leu Lys Ser Lys Lys Ser Ser Glu Phe Tyr Phe His Asn Ile Leu Asn
            1125                1130                1135

aat tta gaa aga gaa aag aaa gat aaa aat ata aag aaa agg aaa aaa   4292
Asn Leu Glu Arg Glu Lys Lys Asp Lys Asn Ile Lys Lys Arg Lys Lys
        1140                1145                1150

tat aat aaa aaa aat ttt aac cct gta tca tta aac aat ata tgt aat   4340
Tyr Asn Lys Lys Asn Phe Asn Pro Val Ser Leu Asn Asn Ile Cys Asn
    1155                1160                1165

ttt tcc ctt aaa tgt tta ggt aat atg aga cat aat aat aat tcc tta   4388
Phe Ser Leu Lys Cys Leu Gly Asn Met Arg His Asn Asn Asn Ser Leu
1170                1175                1180                1185

ttt aaa aat aca tta acg aaa aca gga gaa ata gaa tta aaa tta aaa   4436
Phe Lys Asn Thr Leu Thr Lys Thr Gly Glu Ile Glu Leu Lys Leu Lys
                1190                1195                1200

aaa tgg tta cat tat tta aaa aat tgg ttt tat aaa aaa aaa aga atg   4484
Lys Trp Leu His Tyr Leu Lys Asn Trp Phe Tyr Lys Lys Lys Arg Met
            1205                1210                1215

aaa aag tat att aaa aat aaa tta aaa aac aat aaa aag ata tat gca   4532
Lys Lys Tyr Ile Lys Asn Lys Leu Lys Asn Asn Lys Lys Ile Tyr Ala
        1220                1225                1230

tat ata tgt att gga gat ttc tca aac tgt tat gaa cat ata aat cat   4580
Tyr Ile Cys Ile Gly Asp Phe Ser Asn Cys Tyr Glu His Ile Asn His
    1235                1240                1245

aat tat tta ttc aag att tta aaa aat ttc ttt gat aat ata aat aat   4628
Asn Tyr Leu Phe Lys Ile Leu Lys Asn Phe Phe Asp Asn Ile Asn Asn
1250                1255                1260                1265

ttt gaa ttt att tat tta ttt aaa aga tct ttt aga tta tat aat aaa   4676
Phe Glu Phe Ile Tyr Leu Phe Lys Arg Ser Phe Arg Leu Tyr Asn Lys
                1270                1275                1280

aat tta aat aat tcc ttt tta tcc tat tac cca gtt aat gta aaa tct   4724
Asn Leu Asn Asn Ser Phe Leu Ser Tyr Tyr Pro Val Asn Val Lys Ser
            1285                1290                1295

ttt ggt tta cat tat ata aga aac tta cga gag ctt ata ata aag tca   4772
Phe Gly Leu His Tyr Ile Arg Asn Leu Arg Glu Leu Ile Ile Lys Ser
        1300                1305                1310

cat ctg aat gat aat cat cac ttt tta tta aat caa atg ttt aaa acc   4820
His Leu Asn Asp Asn His His Phe Leu Leu Asn Gln Met Phe Lys Thr
    1315                1320                1325

aaa tca aaa tcg gat tta tac att ttt gcc gat tca tat aaa agt ctg   4868
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Lys Ser Lys Ser Asp Leu Tyr Ile Phe Ala Asp Ser Tyr Lys Ser Leu
1330                1335                1340                1345

caa gtg gac aaa agg gat att ttc atg act ata ata act gtt att aga   4916
Gln Val Asp Lys Arg Asp Ile Phe Met Thr Ile Ile Thr Val Ile Arg
                1350                1355                1360

tat tac tac ctc aat ata tat ttt agt ata aaa gaa ttt aaa ctt aat   4964
Tyr Tyr Tyr Leu Asn Ile Tyr Phe Ser Ile Lys Glu Phe Lys Leu Asn
            1365                1370                1375

agg aaa aat att ttc tat ttt caa ata ttt cag gaa aat caa atg aag   5012
Arg Lys Asn Ile Phe Tyr Phe Gln Ile Phe Gln Glu Asn Gln Met Lys
        1380                1385                1390

ggt gtt tat ttg agt gtc cgt gat aag aaa agg gtt gaa aat att aaa   5060
Gly Val Tyr Leu Ser Val Arg Asp Lys Lys Arg Val Glu Asn Ile Lys
    1395                1400                1405

aaa tgg tat tta aac agc atg aaa aaa ata aat cac gac gaa ata cta   5108
Lys Trp Tyr Leu Asn Ser Met Lys Lys Ile Asn His Asp Glu Ile Leu
1410                1415                1420                1425

gaa agt tta aaa aat tca tcc ata aat ata aat aat aaa aac ttt atg   5156
Glu Ser Leu Lys Asn Ser Ser Ile Asn Ile Asn Asn Lys Asn Phe Met
                1430                1435                1440

ata tgt acc aat cat gag caa gat aca gaa gaa aaa gga aat aca caa   5204
Ile Cys Thr Asn His Glu Gln Asp Thr Glu Glu Lys Gly Asn Thr Gln
            1445                1450                1455

aat aag gag aag cat gat att tat att gga cca ata tat aat aat tcg   5252
Asn Lys Glu Lys His Asp Ile Tyr Ile Gly Pro Ile Tyr Asn Asn Ser
        1460                1465                1470

ttc gac agt aca aca aca aca cat agt agt aat aat tat aaa ggg aat   5300
Phe Asp Ser Thr Thr Thr Thr His Ser Ser Asn Asn Tyr Lys Gly Asn
    1475                1480                1485

aat atc cat gtg agt ggg gat tat aag aat gat ggg cta tta cat aaa   5348
Asn Ile His Val Ser Gly Asp Tyr Lys Asn Asp Gly Leu Leu His Lys
1490                1495                1500                1505

ggt aat aat agt atg aat gaa tgt tat gtg aag gac ata aaa tgt aat   5396
Gly Asn Asn Ser Met Asn Glu Cys Tyr Val Lys Asp Ile Lys Cys Asn
                1510                1515                1520

aat aat aat aat aat aat aat aat aac aac aac aat aat att aat aat   5444
Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Ile Asn Asn
            1525                1530                1535

agt tat aat aaa tta aat tgt gtt acg aat aat agc aaa aat gac ata   5492
Ser Tyr Asn Lys Leu Asn Cys Val Thr Asn Asn Ser Lys Asn Asp Ile
        1540                1545                1550

att aaa tac cac aaa act atc gac aca gat aat agt aaa aat cat aca   5540
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Ile Lys Tyr His Lys Thr Ile Asp Thr Asp Asn Ser Lys Asn His Thr
   1555                1560                1565

tac ttt aaa aat aaa ttc cta aat ttt ttg gat aaa aaa att att agt   5588
Tyr Phe Lys Asn Lys Phe Leu Asn Phe Leu Asp Lys Lys Ile Ile Ser
1570                1575                1580                1585

aat ata tat ggc tta cca caa ggt ttt agc tta tct aat ata ttg tgc   5636
Asn Ile Tyr Gly Leu Pro Gln Gly Phe Ser Leu Ser Asn Ile Leu Cys
               1590                1595                1600

tcc cta tat tat gca tat tta gat aaa aat gaa gaa ttt caa aat tta   5684
Ser Leu Tyr Tyr Ala Tyr Leu Asp Lys Asn Glu Glu Phe Gln Asn Leu
           1605                1610                1615

tta tat tca gaa aaa caa atc aat aat aaa tat ttc tta gca aat gga   5732
Leu Tyr Ser Glu Lys Gln Ile Asn Asn Lys Tyr Phe Leu Ala Asn Gly
       1620                1625                1630

act tgt aat tat ttc aat tta aat tca ctc ata ctc cga ttt att gat   5780
Thr Cys Asn Tyr Phe Asn Leu Asn Ser Leu Ile Leu Arg Phe Ile Asp
   1635                1640                1645

gac ttt tta ttt ata act ctt aat aaa aaa aat att aaa ata ttt aaa   5828
Asp Phe Leu Phe Ile Thr Leu Asn Lys Lys Asn Ile Lys Ile Phe Lys
1650                1655                1660                1665

aac tta cta tta aaa aaa aaa ata tgg gga agt aat att aat tca tcc   5876
Asn Leu Leu Leu Lys Lys Lys Ile Trp Gly Ser Asn Ile Asn Ser Ser
               1670                1675                1680

aaa acc aaa atc ttc aaa ata cca ctt ata tat aaa aat gat tta cta   5924
Lys Thr Lys Ile Phe Lys Ile Pro Leu Ile Tyr Lys Asn Asp Leu Leu
           1685                1690                1695

ata tat aat ttt caa aat aaa tac caa aaa aaa aaa tac aaa ata aaa   5972
Ile Tyr Asn Phe Gln Asn Lys Tyr Gln Lys Lys Lys Tyr Lys Ile Lys
       1700                1705                1710

aat aaa aaa aaa ata caa agt gtg agg aac aaa cgg ata cat aat cag   6020
Asn Lys Lys Lys Ile Gln Ser Val Arg Asn Lys Arg Ile His Asn Gln
   1715                1720                1725

cta gtc aat gct aat aaa aaa aaa cac aca tct gta caa aaa gat aaa   6068
Leu Val Asn Ala Asn Lys Lys Lys His Thr Ser Val Gln Lys Asp Lys
1730                1735                1740                1745

ata aat aaa tat ata aat ctc ata cat cca aca ata caa aaa aat gat   6116
Ile Asn Lys Tyr Ile Asn Leu Ile His Pro Thr Ile Gln Lys Asn Asp
               1750                1755                1760

tct gtc ttg tct tct aat tct att atg aat ttt gaa agg ata tat att   6164
Ser Val Leu Ser Ser Asn Ser Ile Met Asn Phe Glu Arg Ile Tyr Ile
           1765                1770                1775

aaa gaa agt cat aaa agt aac agt tca ata cgt acg gat att ccg aat   6212
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Lys Glu Ser His Lys Ser Asn Ser Ser Ile Arg Thr Asp Ile Pro Asn
       1780                1785                1790

agt gtt gta aat gac gat ata gaa tat aat caa aaa agt gat aat aat   6260
Ser Val Val Asn Asp Asp Ile Glu Tyr Asn Gln Lys Ser Asp Asn Asn
   1795                1800                1805

tct tac agt act aat aat tta tac aac aat ata aat atg act caa aat   6308
Ser Tyr Ser Thr Asn Asn Leu Tyr Asn Asn Ile Asn Met Thr Gln Asn
1810                1815                1820                1825

ggt gat aat aat aat gtt aat att ttt aaa cat gta caa aat gat tct   6356
Gly Asp Asn Asn Asn Val Asn Ile Phe Lys His Val Gln Asn Asp Ser
               1830                1835                1840

ttt caa tgt ttt aat agt aac aac tta tat att gaa aag gat ata aaa   6404
Phe Gln Cys Phe Asn Ser Asn Asn Leu Tyr Ile Glu Lys Asp Ile Lys
           1845                1850                1855

gaa aat aat att tca caa atc aac aga aag tta tgt tct aaa aga aat   6452
Glu Asn Asn Ile Ser Gln Ile Asn Arg Lys Leu Cys Ser Lys Arg Asn
       1860                1865                1870

ttt aca aaa aaa agt aga aaa ata aat act ttg aca tat tta caa att   6500
Phe Thr Lys Lys Ser Arg Lys Ile Asn Thr Leu Thr Tyr Leu Gln Ile
   1875                1880                1885

gat aaa gtt ata aaa atc cta aaa tgt aag aag aaa tat ata aaa cat   6548
Asp Lys Val Ile Lys Ile Leu Lys Cys Lys Lys Lys Tyr Ile Lys His
1890                1895                1900                1905

ata aaa aag atg aag tat atg aat aat ttt caa aat ttt aaa aaa tta   6596
Ile Lys Lys Met Lys Tyr Met Asn Asn Phe Gln Asn Phe Lys Lys Leu
               1910                1915                1920

aaa aaa tta caa aaa ttt cat aat gcc tct ttt gaa tta aaa att aat   6644
Lys Lys Leu Gln Lys Phe His Asn Ala Ser Phe Glu Leu Lys Ile Asn
           1925                1930                1935

aaa att aat aaa aat att aga cga ttg aat aaa tta aaa aaa cgt aaa   6692
Lys Ile Asn Lys Asn Ile Arg Arg Leu Asn Lys Leu Lys Lys Arg Lys
       1940                1945                1950

aat cat tct ata aac att act cct gtt act tct ata gaa tgg tta aat   6740
Asn His Ser Ile Asn Ile Thr Pro Val Thr Ser Ile Glu Trp Leu Asn
   1955                1960                1965

aat tca tac aca ttt gat ttt ata aat aat tct ata caa agc act tca   6788
Asn Ser Tyr Thr Phe Asp Phe Ile Asn Asn Ser Ile Gln Ser Thr Ser
1970                1975                1980                1985

tat cca tgg aaa aat aaa tgt gat gct act att aga aat cat tta cat   6836
Tyr Pro Trp Lys Asn Lys Cys Asp Ala Thr Ile Arg Asn His Leu His
               1990                1995                2000

cta cat aat gtt att ata gat aaa aat aat aaa act tat ttt atg aaa   6884
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Leu His Asn Val Ile Ile Asp Lys Asn Asn Lys Thr Tyr Phe Met Lys
          2005                2010                2015

aac cta gtt gaa aat aga att gta cga aat att ata tcc aaa caa aaa   6932
Asn Leu Val Glu Asn Arg Ile Val Arg Asn Ile Ile Ser Lys Gln Lys
       2020                2025                2030

aaa tgt caa tcc tta tat aag aat aag caa aat gta tat ttc tgt tat   6980
Lys Cys Gln Ser Leu Tyr Lys Asn Lys Gln Asn Val Tyr Phe Cys Tyr
   2035                2040                2045

aaa aat aat ttt agc tta tta aaa tca tct ata tta aaa ttc atc tgt   7028
Lys Asn Asn Phe Ser Leu Leu Lys Ser Ser Ile Leu Lys Phe Ile Cys
2050                2055                2060                2065

tgt att aaa aca ctc aaa aaa atg ttt aat gca ttt aca aat tct aca   7076
Cys Ile Lys Thr Leu Lys Lys Met Phe Asn Ala Phe Thr Asn Ser Thr
               2070                2075                2080

tat aac aca aaa ttt ata tta ttt ctc ata tcg tat atg aat aaa atg   7124
Tyr Asn Thr Lys Phe Ile Leu Phe Leu Ile Ser Tyr Met Asn Lys Met
          2085                2090                2095

tta ata aaa aat aaa aaa ctc aaa ttt gtc aaa ttg ttt tta att caa   7172
Leu Ile Lys Asn Lys Lys Leu Lys Phe Val Lys Leu Phe Leu Ile Gln
       2100                2105                2110

aca gca atc gaa gcc ttc cgt tat gcc aga att ttt aat cag cag gat   7220
Thr Ala Ile Glu Ala Phe Arg Tyr Ala Arg Ile Phe Asn Gln Gln Asp
   2115                2120                2125

tcc ttt tat ccg tgt ctc caa cat ttc agg aaa atc aaa aaa aga tta   7268
Ser Phe Tyr Pro Cys Leu Gln His Phe Arg Lys Ile Lys Lys Arg Leu
2130                2135                2140                2145

att aac aaa tac aaa att gga cat aac aaa aat tta ttg cga gaa ttt   7316
Ile Asn Lys Tyr Lys Ile Gly His Asn Lys Asn Leu Leu Arg Glu Phe
               2150                2155                2160

ttt ttc ctg ttt aat ttt atc aag aaa gag ttg tat aat tca tgg cct   7364
Phe Phe Leu Phe Asn Phe Ile Lys Lys Glu Leu Tyr Asn Ser Trp Pro
          2165                2170                2175

tac atg ttc aaa ata aaa aat taaaaaaaaa aaaaaaaaaa aaaaaatata      7415
Tyr Met Phe Lys Ile Lys Asn
       2180

tatatatata tatatatata tatatataag tataaacgtt gtttatatta atatgtccaa 7475

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ttctattatt ttttttttt tttgcatttg tatttgtttt taaatatata ttgattttgg 7595

attgacatat ttttttttta ttttttcttt ttttttataa tcttggcttg gtgtccaaac 7655

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ccaatccttt tttattaata ttataaaggg tatgtgatat attcttgtaa taatttggct 7775

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gttcgagaac tcttgaagct ctccatttga atggtctaat attactataa taatttttat 7895

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cgatacaaag atactaaata ataaaaaaat atatataaat catatatata ttatttaat 10535

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20 25 30

Tyr Gln Asn Asn Val Asn Thr His Ile Tyr Ser Asn Asp Asn Lys Thr

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         35                  40                  45

Pro Ile Ile Ala Asn Gln Cys Ile Asp Ile His Asn Arg Val Ser Asp
     50                  55                  60

Pro Thr Arg Lys Asn Ile Phe Tyr His Ser Ile Asn Ser Leu Ser Tyr
 65                  70                  75                  80

Glu Ala Ser Leu Asn Ile Phe His Tyr Asn Asn Leu Thr Gln His Thr
                 85                  90                  95

Thr Tyr Ile Asp Thr Pro Asn Lys Ser Gln Thr Cys Ile Asn Ser Pro
            100                 105                 110

Met Gln His Glu Ile Asp Glu His Ser Asn Asn Glu Leu Lys Asn Gln
        115                 120                 125

Lys Cys Thr Gln Tyr Glu Tyr Val Asp Asn Val Cys Thr Thr Asn Lys
    130                 135                 140

Asn Ile Ser Asn Asp Asn Ile Ser Asp Lys Cys Ile Thr Thr Lys Asn
145                 150                 155                 160

Ile Pro Leu Lys Tyr His Ile Asn Lys Lys Tyr Lys Tyr Leu Leu Lys
                165                 170                 175

Lys Lys Tyr His Thr Met Tyr Thr Asn Asn Asp His Ser Tyr Gly Lys
            180                 185                 190

Tyr Leu Tyr Leu Val Gln Cys Ser Gly Arg Ile Leu Lys Asn Asp Phe
        195                 200                 205

Phe Lys Asp Met Lys Gln Ile Gln Glu Glu Arg Lys Lys Tyr Thr Ser
    210                 215                 220

Asn Ile Lys Ile Asn Ser Glu Tyr Thr Asn Asn Ile Ile Ile Asn Asn
225                 230                 235                 240

Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Val His
                245                 250                 255

Gly Phe Gly His Ile Asn Asn Leu Phe Ser Ser Asn Glu Phe Pro Ser
            260                 265                 270

Ser Asn Ile Ser Ser Cys Thr Asn Tyr Thr Glu Lys Asn Asp Lys Leu
        275                 280                 285

Thr His Ile Arg Glu Thr Ser Leu Leu Ile Thr Glu Asn Ser Ser Lys
    290                 295                 300

Lys Asp Lys Leu Leu Pro Glu Ile Asp Phe Phe Ser Glu Asp Arg Lys
305                 310                 315                 320

Glu Lys Ser Ser Ser Val Gly Tyr Asp Xaa Lys Lys Lys Asn Xaa Ser
                325                 330                 335
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Asn Ile Lys Arg Phe His Asn Lys Ile Asn Arg Thr Lys Glu Glu Lys
            340                 345                 350

Lys Lys Lys Trp Asn Lys Ile Ile Ile Asn Arg Asn Asn Ile Leu Gln
        355                 360                 365

His Asn Thr Thr Asn Lys Cys Lys Thr Phe Leu Phe Asn Lys His Ile
    370                 375                 380

Ile Phe Asp Lys Ile Glu Asn Asn Asn Ile Pro Leu Phe Ile Tyr Asp
385                 390                 395                 400

Leu Leu Asn Tyr Ile Phe Lys Ser Asp Gln Thr Tyr Phe Tyr His Asn
                405                 410                 415

Asn Phe Ile Asp Glu Tyr Lys Gln Lys Ile Cys Lys Gln Ile Lys Cys
            420                 425                 430

Ser Thr Lys Lys Asn Asp Ile Ser His Ile Ile Thr Ser Arg Lys Glu
        435                 440                 445

Asn His Leu Phe His Val Gln Lys Leu Glu Asn Asn Tyr Lys His Pro
    450                 455                 460

Asn Ile Asn Lys Gln Leu Arg Lys Thr Lys Ile Leu Lys Tyr Val Tyr
465                 470                 475                 480

Asn Tyr Phe Lys Glu Phe Ile Asn Asn Val Ile Asn Thr Lys Phe Gly
                485                 490                 495

Lys Ile Tyr Arg Lys Phe Phe Pro Arg Lys His Ile Leu Asn Lys Ile
            500                 505                 510

His Lys Ile Phe Lys Ile Ile Arg Leu Gln Ile Ile Lys Lys Tyr Arg
        515                 520                 525

Ile Ile Asn Ile Arg Met Asn Arg Lys Phe Ile Lys Gln Lys Val Tyr
    530                 535                 540

Asp Thr Phe Phe Lys Asn Tyr Asp Phe Leu Ser Phe Ser Phe Lys Thr
545                 550                 555                 560

Tyr Lys Ile Ile Asn Phe Met Val Tyr Ile Thr Lys Lys Cys Ile Pro
                565                 570                 575

Ile Lys Leu Leu Gly Ser Lys His Asn Phe Lys Ile Phe Leu Lys Asn
            580                 585                 590

Val Lys Lys Phe Leu Leu Phe Asn Tyr Lys Glu Ser Phe Ser Leu Asn
        595                 600                 605

Gln Val Met Lys Asn Ile Lys Val Lys Asn Ile Phe Gln Lys Lys Ile
    610                 615                 620

Ser Lys Tyr Asn Ile Lys Asn Arg Ile Leu Leu Lys Asn Ile Phe Asp
625                 630                 635                 640
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Asn Asn Tyr Glu Asn Lys Ile Leu His Arg Asn Asn Lys Glu Ile Ile
645 650 655

Thr Asn Ile Asn Asp Asn Ile Lys Ile Tyr Asn Lys Lys Asn Asp Asn
660 665 670

Leu Asn Asn Ser Phe Lys Ile Lys Thr Thr Leu Phe Asn Lys Leu Arg
675 680 685

Arg Lys Tyr Phe Asn Lys Ile Lys Lys Ile Asn Ile Ala Ile Gln Lys
690 695 700

Arg His Leu Met Asn Arg Leu Ile Tyr Phe Leu Phe Asn Tyr Phe Ile
705 710 715 720

Met Pro Leu Ile Arg Arg Phe Phe Phe Leu Thr Lys Ser Glu Gln Thr
725 730 735

Leu His Lys Thr Ile Phe Phe Asp Arg Lys Ile Trp Asn His Phe Thr
740 745 750

Lys Ile Ser Asn Phe Cys Leu Tyr His Gln Ile Phe Arg Asn Lys Lys
755 760 765

Leu Lys Lys Arg Asn Glu Pro Lys Met Asp Tyr Val Gln Asn Met Phe
770 775 780

Asn Val Lys Lys Lys Gly Glu Lys Ile Lys Thr Asn Lys Tyr Ile Phe
785 790 795 800

Ile Lys Lys Met Lys Lys Lys Ser Thr Asn Lys Cys Ile Asn Asn Lys
805 810 815

Phe Ser Lys Lys Cys Ile Pro Lys Lys Lys Lys Lys Asn Leu Tyr Asn
820 825 830

Ile Thr Arg His Asn Asn Ile Phe Ile Lys Lys Asp Met Glu Lys Lys
835 840 845

Ser Lys Thr Asn Asn Leu Ile Asn Lys Ser Ile Asp Asn Leu Tyr Lys
850 855 860

Leu Lys Glu Ile Asn Lys Lys Ser Val Arg Pro Tyr Ile Lys Lys Phe
865 870 875 880

Tyr Tyr Lys Ile Lys Lys Lys Tyr Phe Ala Leu Lys Lys Met Tyr Ile
885 890 895

His Met Arg Met Ala Lys Glu Glu Lys Ser Asn Ile Lys Leu Glu Arg
900 905 910

Ala Phe Lys His Phe Phe Ile Phe Ala Gln Glu Lys Glu His Ile Leu
915 920 925

Lys Tyr Phe Ser Ser His Phe Phe Gln Asn Arg Lys Ile Asn Tyr Gly
930 935 940

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Lys Arg Phe Asn Lys Leu Ile His Arg Ile Lys Asn Ile Ile Ile Lys
945                 950                 955                 960

Gln Asn Ser Gly Ile Val Lys Asn Lys Asp Lys Thr Phe Leu His Leu
                965                 970                 975

Ile Lys Asn Lys Ser Asn Lys Asn Asn Asn Asn Lys Lys Lys Asn Lys
            980                 985                 990

Asn Asn Tyr Asn Asn Asn Asn Ile Asn Asn Asn Asn Asn Asn Asn Asn
        995                1000                1005

Asn Asn Asn Ile Asn Asn Asn Asn Asn Asn Lys Cys Lys Leu Ser Asn
   1010                1015                1020

Ser Lys Arg Tyr Asn Ile Arg Asn Asn Asn Asn Asn Lys Lys Ala Lys
1025                1030                1035                1040

Asn Asn Glu Lys Asn Asn Ile Asp Asp Ser Asn Leu Glu Lys Lys Lys
               1045                1050                1055

Lys Lys Ile Tyr Ile Tyr Lys Ile Lys Asn Ile Ile Glu Lys Arg Asn
           1060                1065                1070

Phe Met Leu Lys Leu Asn Ser Ile Asn His Phe Ile Ser Lys Lys Leu
       1075                1080                1085

Arg Ile Asn Trp Ile Pro Lys Lys Lys Gly Leu Arg Pro Leu Ile Asn
   1090                1095                1100

Leu Ser Thr Leu Asn Val Pro Glu Ile Val Lys Gln Arg Ile Phe Glu
1105                1110                1115                1120

Ile Leu Lys Ser Lys Lys Ser Ser Glu Phe Tyr Phe His Asn Ile Leu
               1125                1130                1135

Asn Asn Leu Glu Arg Glu Lys Lys Asp Lys Asn Ile Lys Lys Arg Lys
           1140                1145                1150

Lys Tyr Asn Lys Lys Asn Phe Asn Pro Val Ser Leu Asn Asn Ile Cys
       1155                1160                1165

Asn Phe Ser Leu Lys Cys Leu Gly Asn Met Arg His Asn Asn Asn Ser
   1170                1175                1180

Leu Phe Lys Asn Thr Leu Thr Lys Thr Gly Glu Ile Glu Leu Lys Leu
1185                1190                1195                1200

Lys Lys Trp Leu His Tyr Leu Lys Asn Trp Phe Tyr Lys Lys Lys Arg
               1205                1210                1215

Met Lys Lys Tyr Ile Lys Asn Lys Leu Lys Asn Asn Lys Lys Ile Tyr
           1220                1225                1230

Ala Tyr Ile Cys Ile Gly Asp Phe Ser Asn Cys Tyr Glu His Ile Asn
       1235                1240                1245
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Ile Ile Lys Tyr His Lys Thr Ile Asp Thr Asp Asn Ser Lys Asn His
       1555                1560                1565

Thr Tyr Phe Lys Asn Lys Phe Leu Asn Phe Leu Asp Lys Lys Ile Ile
   1570                1575                1580

Ser Asn Ile Tyr Gly Leu Pro Gln Gly Phe Ser Leu Ser Asn Ile Leu
1585                1590                1595                1600

Cys Ser Leu Tyr Tyr Ala Tyr Leu Asp Lys Asn Glu Glu Phe Gln Asn
               1605                1610                1615

Leu Leu Tyr Ser Glu Lys Gln Ile Asn Asn Lys Tyr Phe Leu Ala Asn
           1620                1625                1630

Gly Thr Cys Asn Tyr Phe Asn Leu Asn Ser Leu Ile Leu Arg Phe Ile
       1635                1640                1645

Asp Asp Phe Leu Phe Ile Thr Leu Asn Lys Lys Asn Ile Lys Ile Phe
   1650                1655                1660

Lys Asn Leu Leu Leu Lys Lys Lys Ile Trp Gly Ser Asn Ile Asn Ser
1665                1670                1675                1680

Ser Lys Thr Lys Ile Phe Lys Ile Pro Leu Ile Tyr Lys Asn Asp Leu
               1685                1690                1695

Leu Ile Tyr Asn Phe Gln Asn Lys Tyr Gln Lys Lys Lys Tyr Lys Ile
           1700                1705                1710

Lys Asn Lys Lys Lys Ile Gln Ser Val Arg Asn Lys Arg Ile His Asn
       1715                1720                1725

Gln Leu Val Asn Ala Asn Lys Lys Lys His Thr Ser Val Gln Lys Asp
   1730                1735                1740

Lys Ile Asn Lys Tyr Ile Asn Leu Ile His Pro Thr Ile Gln Lys Asn
1745                1750                1755                1760

Asp Ser Val Leu Ser Ser Asn Ser Ile Met Asn Phe Glu Arg Ile Tyr
               1765                1770                1775

Ile Lys Glu Ser His Lys Ser Asn Ser Ser Ile Arg Thr Asp Ile Pro
           1780                1785                1790

Asn Ser Val Val Asn Asp Asp Ile Glu Tyr Asn Gln Lys Ser Asp Asn
       1795                1800                1805

Asn Ser Tyr Ser Thr Asn Asn Leu Tyr Asn Asn Ile Asn Met Thr Gln
   1810                1815                1820

Asn Gly Asp Asn Asn Asn Val Asn Ile Phe Lys His Val Gln Asn Asp
1825                1830                1835                1840

Ser Phe Gln Cys Phe Asn Ser Asn Asn Leu Tyr Ile Glu Lys Asp Ile
               1845                1850                1855
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Lys Glu Asn Asn Ile Ser Gln Ile Asn Arg Lys Leu Cys Ser Lys Arg
            1860                1865                1870

Asn Phe Thr Lys Lys Ser Arg Lys Ile Asn Thr Leu Thr Tyr Leu Gln
        1875                1880                1885

Ile Asp Lys Val Ile Lys Ile Leu Lys Cys Lys Lys Lys Tyr Ile Lys
    1890                1895                1900

His Ile Lys Lys Met Lys Tyr Met Asn Asn Phe Gln Asn Phe Lys Lys
1905                1910                1915                1920

Leu Lys Lys Leu Gln Lys Phe His Asn Ala Ser Phe Glu Leu Lys Ile
                1925                1930                1935

Asn Lys Ile Asn Lys Asn Ile Arg Arg Leu Asn Lys Leu Lys Lys Arg
            1940                1945                1950

Lys Asn His Ser Ile Asn Ile Thr Pro Val Thr Ser Ile Glu Trp Leu
        1955                1960                1965

Asn Asn Ser Tyr Thr Phe Asp Phe Ile Asn Asn Ser Ile Gln Ser Thr
    1970                1975                1980

Ser Tyr Pro Trp Lys Asn Lys Cys Asp Ala Thr Ile Arg Asn His Leu
1985                1990                1995                2000

His Leu His Asn Val Ile Ile Asp Lys Asn Asn Lys Thr Tyr Phe Met
                2005                2010                2015

Lys Asn Leu Val Glu Asn Arg Ile Val Arg Asn Ile Ile Ser Lys Gln
            2020                2025                2030

Lys Lys Cys Gln Ser Leu Tyr Lys Asn Lys Gln Asn Val Tyr Phe Cys
        2035                2040                2045

Tyr Lys Asn Asn Phe Ser Leu Leu Lys Ser Ser Ile Leu Lys Phe Ile
    2050                2055                2060

Cys Cys Ile Lys Thr Leu Lys Lys Met Phe Asn Ala Phe Thr Asn Ser
2065                2070                2075                2080

Thr Tyr Asn Thr Lys Phe Ile Leu Phe Leu Ile Ser Tyr Met Asn Lys
                2085                2090                2095

Met Leu Ile Lys Asn Lys Lys Leu Lys Phe Val Lys Leu Phe Leu Ile
            2100                2105                2110

Gln Thr Ala Ile Glu Ala Phe Arg Tyr Ala Arg Ile Phe Asn Gln Gln
        2115                2120                2125

Asp Ser Phe Tyr Pro Cys Leu Gln His Phe Arg Lys Ile Lys Lys Arg
    2130                2135                2140

Leu Ile Asn Lys Tyr Lys Ile Gly His Asn Lys Asn Leu Leu Arg Glu
2145                2150                2155                2160
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Pro Tyr Met Phe Lys Ile Lys Asn
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  1               5                  10                  15

att aaa aaa tgg tat tta aac agc atg aaa aaa ata aat cac gac gaa   96
Ile Lys Lys Trp Tyr Leu Asn Ser Met Lys Lys Ile Asn His Asp Glu
             20                  25                  30

ata cta gaa agt tta aaa aat tca tcc ata aat ata aat aat aaa aac   144
Ile Leu Glu Ser Leu Lys Asn Ser Ser Ile Asn Ile Asn Asn Lys Asn
         35                  40                  45

ttt atg ata tgt acc aat cat gag caa gat aca gaa gaa aaa gga aat   192
Phe Met Ile Cys Thr Asn His Glu Gln Asp Thr Glu Glu Lys Gly Asn
     50                  55                  60

aca caa aat aag gag aag cat gat att tat att gga cca ata tat aat   240
Thr Gln Asn Lys Glu Lys His Asp Ile Tyr Ile Gly Pro Ile Tyr Asn
 65                  70                  75                  80

aat tcg ttc gac agt aca aca aca aca cat agt agt aat aat tat aaa   288
Asn Ser Phe Asp Ser Thr Thr Thr Thr His Ser Ser Asn Asn Tyr Lys
                 85                  90                  95

ggg aat aat atc cat gtg agt ggg gat tat aag aat gat ggg cta tta   336
Gly Asn Asn Ile His Val Ser Gly Asp Tyr Lys Asn Asp Gly Leu Leu
            100                 105                 110

cat aaa ggt aat aat agt atg aat gaa tgt tat gtg aag gac ata aaa   384
His Lys Gly Asn Asn Ser Met Asn Glu Cys Tyr Val Lys Asp Ile Lys
        115                 120                 125

tgt aat aat aat aat aat aat aat aat aat aat aac aac aac aat aat att   432
Cys Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Ile
    130                 135                 140

aat aat agt tat aat aaa tta aat tgt gtt acg aat aat agc aaa aat   480
```

```
Asn Asn Ser Tyr Asn Lys Leu Asn Cys Val Thr Asn Asn Ser Lys Asn
145                 150                 155                 160

gac ata att aaa tac cac aaa act atc gac aca gat aat agt aaa aat   528
Asp Ile Ile Lys Tyr His Lys Thr Ile Asp Thr Asp Asn Ser Lys Asn
                165                 170                 175

cat aca tac ttt aaa aat aaa ttc cta aat ttt ttg gat aaa aaa att   576
His Thr Tyr Phe Lys Asn Lys Phe Leu Asn Phe Leu Asp Lys Lys Ile
            180                 185                 190

att agt aat ata tat ggc tta cca caa ggt ttt agc tta tct aat ata   624
Ile Ser Asn Ile Tyr Gly Leu Pro Gln Gly Phe Ser Leu Ser Asn Ile
        195                 200                 205

ttg tgc tcc cta tat tat gca tat cta gat aaa aat gaa gaa tct caa   672
Leu Cys Ser Leu Tyr Tyr Ala Tyr Leu Asp Lys Asn Glu Glu Ser Gln
    210                 215                 220

aat tta tta tat tca gaa aaa caa atc aat aat aaa tat ttc tta gca   720
Asn Leu Leu Tyr Ser Glu Lys Gln Ile Asn Asn Lys Tyr Phe Leu Ala
225                 230                 235                 240

aat gga act tgt aat tat ttc aat tta aat tca ctc ata ctc cga ttt   768
Asn Gly Thr Cys Asn Tyr Phe Asn Leu Asn Ser Leu Ile Leu Arg Phe
                245                 250                 255

att gat gac ttt tta ttt ata act ctt aat aaa aaa aat att aaa ata   816
Ile Asp Asp Phe Leu Phe Ile Thr Leu Asn Lys Lys Asn Ile Lys Ile
            260                 265                 270

ttt aaa aac tta cta tta aaa aaa aaa ata tgg gga agt aat att aat   864
Phe Lys Asn Leu Leu Leu Lys Lys Lys Ile Trp Gly Ser Asn Ile Asn
        275                 280                 285

tca tcc aaa acc aaa atc ttc aaa ata cca ctt ata tat aaa aat gat   912
Ser Ser Lys Thr Lys Ile Phe Lys Ile Pro Leu Ile Tyr Lys Asn Asp
    290                 295                 300

tta cta ata tat aat ttt caa aat aaa tac caa caa aaa aaa aaa tac   960
Leu Leu Ile Tyr Asn Phe Gln Asn Lys Tyr Gln Gln Lys Lys Lys Tyr
305                 310                 315                 320

aaa ata aaa aat aaa aaa aaa ata caa agt gtg agg aac aaa cgg ata   1008
Lys Ile Lys Asn Lys Lys Lys Ile Gln Ser Val Arg Asn Lys Arg Ile
                325                 330                 335

cat aat cag cta gtc aat gct aat aaa aaa aaa cac aca tct gta caa   1056
His Asn Gln Leu Val Asn Ala Asn Lys Lys Lys His Thr Ser Val Gln
            340                 345                 350

aaa gat aaa ata aat aaa tat ata aat ctc ata cat cca aca ata caa   1104
Lys Asp Lys Ile Asn Lys Tyr Ile Asn Leu Ile His Pro Thr Ile Gln
        355                 360                 365

aaa aat gat tct gtc ttg tct tct aat tct att atg aat ttt gaa agg   1152
```

```
Lys Asn Asp Ser Val Leu Ser Ser Asn Ser Ile Met Asn Phe Glu Arg
    370                 375                 380

ata tat aat aaa gaa agt cat aaa agt aac agt tca ata cgt acg gat   1200
Ile Tyr Asn Lys Glu Ser His Lys Ser Asn Ser Ser Ile Arg Thr Asp
385                 390                 395                 400

att ccg aat agt gtt gta aat gac gat ata gaa tat aat caa aaa agt   1248
Ile Pro Asn Ser Val Val Asn Asp Asp Ile Glu Tyr Asn Gln Lys Ser
                405                 410                 415

gat aat aat tct tac agt act aat aat tta tac aac aat ata aat atg   1296
Asp Asn Asn Ser Tyr Ser Thr Asn Asn Leu Tyr Asn Asn Ile Asn Met
            420                 425                 430

act caa aat ggt gat aat aat aat gtt aat att ttt aaa cat gta caa   1344
Thr Gln Asn Gly Asp Asn Asn Asn Val Asn Ile Phe Lys His Val Gln
        435                 440                 445

aat gat tct ttt caa tgt ttt aat agt aac aac tta tat att gaa aag   1392
Asn Asp Ser Phe Gln Cys Phe Asn Ser Asn Asn Leu Tyr Ile Glu Lys
    450                 455                 460

gat ata aaa gaa aat aat att tca caa atc aac aga aag tta tgt act   1440
Asp Ile Lys Glu Asn Asn Ile Ser Gln Ile Asn Arg Lys Leu Cys Thr
465                 470                 475                 480

aaa aga aat ttt aca aaa aaa agt aga aaa ata aat act gtg aca tat   1488
Lys Arg Asn Phe Thr Lys Lys Ser Arg Lys Ile Asn Thr Val Thr Tyr
                485                 490                 495

cta caa att gat aaa gtt ata aaa atc cta aaa tgt aag aag aaa tat   1536
Leu Gln Ile Asp Lys Val Ile Lys Ile Leu Lys Cys Lys Lys Lys Tyr
            500                 505                 510

ata aaa cat ata aaa aag atg aag tat atg aat aat ttt caa aat ttt   1584
Ile Lys His Ile Lys Lys Met Lys Tyr Met Asn Asn Phe Gln Asn Phe
        515                 520                 525

aaa aaa tta aaa aaa tta caa aaa ttt caa aat gcc tct ttt gaa tta   1632
Lys Lys Leu Lys Lys Leu Gln Lys Phe Gln Asn Ala Ser Phe Glu Leu
    530                 535                 540

aaa att aat aaa att aat aaa aat att aga cga ttg aat aaa tta aaa   1680
Lys Ile Asn Lys Ile Asn Lys Asn Ile Arg Arg Leu Asn Lys Leu Lys
545                 550                 555                 560

aaa cgt aaa aat cat tct ata aac att act cct gtt act tct ata gaa   1728
Lys Arg Lys Asn His Ser Ile Asn Ile Thr Pro Val Thr Ser Ile Glu
                565                 570                 575

tgg tta aat aat tca tac aca ttt gat ttt ata aat aat tct ata caa   1776
Trp Leu Asn Asn Ser Tyr Thr Phe Asp Phe Ile Asn Asn Ser Ile Gln
            580                 585                 590

agc act tca tat cca tgg aaa aat aaa tgt gat gct act att aga aat   1824
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```
Ser Thr Ser Tyr Pro Trp Lys Asn Lys Cys Asp Ala Thr Ile Arg Asn
        595                 600                 605

cat tta cat cta cat aat gtt att ata gat aaa aat aat aaa act tat   1872
His Leu His Leu His Asn Val Ile Ile Asp Lys Asn Asn Lys Thr Tyr
    610                 615                 620

ttt atg aaa aac cta gtt gaa aat aga att gta cga aat att ata tcc   1920
Phe Met Lys Asn Leu Val Glu Asn Arg Ile Val Arg Asn Ile Ile Ser
625                 630                 635                 640

aaa caa aaa aaa tgt caa tcc tta tat aag aat aag caa aat gta tat   1968
Lys Gln Lys Lys Cys Gln Ser Leu Tyr Lys Asn Lys Gln Asn Val Tyr
                645                 650                 655

ttc tgt tat aaa aat aat ttt agc tta tta aaa tca tct ata tta aaa   2016
Phe Cys Tyr Lys Asn Asn Phe Ser Leu Leu Lys Ser Ser Ile Leu Lys
            660                 665                 670

ttc atc tgt tgt att aaa aca ctc aaa aaa atg ttt aat gca ttt aca   2064
Phe Ile Cys Cys Ile Lys Thr Leu Lys Lys Met Phe Asn Ala Phe Thr
        675                 680                 685

aat tct aca tat aac aca aaa ttt ata tta ttt ctc ata tcg tat atg   2112
Asn Ser Thr Tyr Asn Thr Lys Phe Ile Leu Phe Leu Ile Ser Tyr Met
    690                 695                 700

aat aaa atg tta ata aaa aat aaa aaa ctc aaa ttt gtc aaa ttg ttt   2160
Asn Lys Met Leu Ile Lys Asn Lys Lys Leu Lys Phe Val Lys Leu Phe
705                 710                 715                 720

tta att caa aca gca atc gaa gcc ttc cgt tat gcc aga att ttt aat   2208
Leu Ile Gln Thr Ala Ile Glu Ala Phe Arg Tyr Ala Arg Ile Phe Asn
                725                 730                 735

cag cag gat tcc ttt tat ccg tgt ctc caa cat ttc agg aaa atc aaa   2256
Gln Gln Asp Ser Phe Tyr Pro Cys Leu Gln His Phe Arg Lys Ile Lys
            740                 745                 750

aaa aga tta att aac aaa tac aaa att gga cat aac aaa aat tta ttg   2304
Lys Arg Leu Ile Asn Lys Tyr Lys Ile Gly His Asn Lys Asn Leu Leu
        755                 760                 765

cga gaa ttt ttt ttc ctg ttt aat ttt atc aag aaa gag ttg tat aat   2352
Arg Glu Phe Phe Phe Leu Phe Asn Phe Ile Lys Lys Glu Leu Tyr Asn
    770                 775                 780

tca tgg cct tac atg ttc aaa ata aaa aat taaaaaaaaa aaaaaaaaaa     2402
Ser Trp Pro Tyr Met Phe Lys Ile Lys Asn
785                 790

aaaaaaatat atatatatat atatatatat atatatataa gtataaacgt tgtttatatt 2462

aatatgtcca acttataaag ttatataatt attaattttg ttcatatttt acttaatatt 2522

aattttatac attctattat ttttttttt ttttgcattt gtatttgttt ttaaatatat 2582
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attgattttg gattgacata ttttttttt attttttctt ttttttata atcttggctt 2642

ggtgtccaaa catagattgg atatttttt cagagcctgc aactttccac gtgaacctac 2702

cctaatattt accaatcctt ttttattaat attataaagg gtatgtgata tattcttgta 2762

ataatttggc ttgaaaccat actgataaga acttggttct ccagattttt tataaagcaa 2822

aaatggatat ggttcgagaa ctcttgaagc tctccatttg aatggtctaa tattactata 2882

ataattttta tattttcttc ttataattcc atgatatttt ttaaatgaaa ttttattatg 2942

ccttctacaa aaataaataa cattagatgg tatttctaat aatcttctat taaccatatt 3002

ccaatatttt ggtgcaggca ttacttttt atgtggtaaa taatttcttg aaacttcttc 3062

aagagcctca ctatatattt tacatgtatt gtaatcttta tcaacaaatg atatagaatt 3122

tatattatat aatggaatgg tacttcttag ttgtaataat gattcaacac attcctcaag 3182

taatatatta ctagattgat tcggactata tccatatata cctgctgaga tatccggtaa 3242

tattatagaa gatatacata actcattcaa ttgttttaaa gcattagaaa agcaatatct 3302

taacttattt gatgaaatat atgaattacc ctgccataca tatggcatta ttaaaaatgc 3362

taataatttc actttttac taacattatg tggtttactt aatataatat caccaatttg 3422

taatgttttt gatccttcat ataattcttt aaatttttgt tctccattta tttctaaaga 3482

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tttaattgat agaattatct ctttaactaa ttcgggaccc cctttattta atataaacga 3602

accaaaacca ctcataggta tgaaattaga aaccataggt attaacatac aatctgcttc 3662

ttcatctata atatcattat gtattatttt aatattacca aattcttcta aagtcatatt 3722

tttcatttca tattcatatt tatccttaat tttatttata tctaatatat ccatatcttc 3782

ttctaataaa cctttattct catcattctc cttattattt aaaaaaaaca tatcatttat 3842

ctcacttttc atgttaggaa atatttcttt cattacactt ctattcttcc gttctaatat 3902

atcgagagat ttcgtataat ctatatgata ttttaatgct ctttcgttta ttgttttcaa 3962

cctcttggtt aaataggaac taccaaaata acgtttcccc ataaaaaaaa atcttaacat 4022

ttttatatat acccataata atatacaaat aaataaatat atatatatat atatatatgt 4082

atcagtctat actacatggg gttaatgata gaaaaatata ttaaaaatat atttatatac 4142

ttttataaat aggatatata gattattttg atctaaaatg aca 4185

<210> 8

<211> 794
<212> PRT
<213> Plasmodium falciparum

<400> 8

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Met Lys Gly Val Tyr Leu Gly Ala Arg Asp Lys Lys Arg Val Glu Asn
  1               5                  10                  15

Ile Lys Lys Trp Tyr Leu Asn Ser Met Lys Lys Ile Asn His Asp Glu
             20                  25                  30

Ile Leu Glu Ser Leu Lys Asn Ser Ser Ile Asn Ile Asn Asn Lys Asn
         35                  40                  45

Phe Met Ile Cys Thr Asn His Glu Gln Asp Thr Glu Glu Lys Gly Asn
     50                  55                  60

Thr Gln Asn Lys Glu Lys His Asp Ile Tyr Ile Gly Pro Ile Tyr Asn
 65                  70                  75                  80

Asn Ser Phe Asp Ser Thr Thr Thr Thr His Ser Ser Asn Asn Tyr Lys
                 85                  90                  95

Gly Asn Asn Ile His Val Ser Gly Asp Tyr Lys Asn Asp Gly Leu Leu
            100                 105                 110

His Lys Gly Asn Asn Ser Met Asn Glu Cys Tyr Val Lys Asp Ile Lys
        115                 120                 125

Cys Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Ile
    130                 135                 140

Asn Asn Ser Tyr Asn Lys Leu Asn Cys Val Thr Asn Asn Ser Lys Asn
145                 150                 155                 160

Asp Ile Ile Lys Tyr His Lys Thr Ile Asp Thr Asp Asn Ser Lys Asn
                165                 170                 175

His Thr Tyr Phe Lys Asn Lys Phe Leu Asn Phe Leu Asp Lys Lys Ile
            180                 185                 190

Ile Ser Asn Ile Tyr Gly Leu Pro Gln Gly Phe Ser Leu Ser Asn Ile
        195                 200                 205

Leu Cys Ser Leu Tyr Tyr Ala Tyr Leu Asp Lys Asn Glu Glu Ser Gln
    210                 215                 220

Asn Leu Leu Tyr Ser Glu Lys Gln Ile Asn Asn Lys Tyr Phe Leu Ala
225                 230                 235                 240

Asn Gly Thr Cys Asn Tyr Phe Asn Leu Asn Ser Leu Ile Leu Arg Phe
                245                 250                 255

Ile Asp Asp Phe Leu Phe Ile Thr Leu Asn Lys Lys Asn Ile Lys Ile
            260                 265                 270
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Phe Lys Asn Leu Leu Leu Lys Lys Lys Ile Trp Gly Ser Asn Ile Asn
        275                 280                 285

Ser Ser Lys Thr Lys Ile Phe Lys Ile Pro Leu Ile Tyr Lys Asn Asp
    290                 295                 300

Leu Leu Ile Tyr Asn Phe Gln Asn Lys Tyr Gln Gln Lys Lys Lys Tyr
305                 310                 315                 320

Lys Ile Lys Asn Lys Lys Lys Ile Gln Ser Val Arg Asn Lys Arg Ile
                325                 330                 335

His Asn Gln Leu Val Asn Ala Asn Lys Lys Lys His Thr Ser Val Gln
            340                 345                 350

Lys Asp Lys Ile Asn Lys Tyr Ile Asn Leu Ile His Pro Thr Ile Gln
        355                 360                 365

Lys Asn Asp Ser Val Leu Ser Ser Asn Ser Ile Met Asn Phe Glu Arg
    370                 375                 380

Ile Tyr Asn Lys Glu Ser His Lys Ser Asn Ser Ser Ile Arg Thr Asp
385                 390                 395                 400

Ile Pro Asn Ser Val Val Asn Asp Asp Ile Glu Tyr Asn Gln Lys Ser
                405                 410                 415

Asp Asn Asn Ser Tyr Ser Thr Asn Asn Leu Tyr Asn Asn Ile Asn Met
            420                 425                 430

Thr Gln Asn Gly Asp Asn Asn Asn Val Asn Ile Phe Lys His Val Gln
        435                 440                 445

Asn Asp Ser Phe Gln Cys Phe Asn Ser Asn Asn Leu Tyr Ile Glu Lys
    450                 455                 460

Asp Ile Lys Glu Asn Asn Ile Ser Gln Ile Asn Arg Lys Leu Cys Thr
465                 470                 475                 480

Lys Arg Asn Phe Thr Lys Lys Ser Arg Lys Ile Asn Thr Val Thr Tyr
                485                 490                 495

Leu Gln Ile Asp Lys Val Ile Lys Ile Leu Lys Cys Lys Lys Lys Tyr
            500                 505                 510

Ile Lys His Ile Lys Lys Met Lys Tyr Met Asn Asn Phe Gln Asn Phe
        515                 520                 525

Lys Lys Leu Lys Lys Leu Gln Lys Phe Gln Asn Ala Ser Phe Glu Leu
    530                 535                 540

Lys Ile Asn Lys Ile Asn Lys Asn Ile Arg Arg Leu Asn Lys Leu Lys
545                 550                 555                 560

Lys Arg Lys Asn His Ser Ile Asn Ile Thr Pro Val Thr Ser Ile Glu
                565                 570                 575
```

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Trp Leu Asn Asn Ser Tyr Thr Phe Asp Phe Ile Asn Asn Ser Ile Gln
            580                 585                 590

Ser Thr Ser Tyr Pro Trp Lys Asn Lys Cys Asp Ala Thr Ile Arg Asn
        595                 600                 605

His Leu His Leu His Asn Val Ile Ile Asp Lys Asn Asn Lys Thr Tyr
    610                 615                 620

Phe Met Lys Asn Leu Val Glu Asn Arg Ile Val Arg Asn Ile Ile Ser
625                 630                 635                 640

Lys Gln Lys Lys Cys Gln Ser Leu Tyr Lys Asn Lys Gln Asn Val Tyr
                645                 650                 655

Phe Cys Tyr Lys Asn Asn Phe Ser Leu Leu Lys Ser Ser Ile Leu Lys
            660                 665                 670

Phe Ile Cys Cys Ile Lys Thr Leu Lys Lys Met Phe Asn Ala Phe Thr
        675                 680                 685

Asn Ser Thr Tyr Asn Thr Lys Phe Ile Leu Phe Leu Ile Ser Tyr Met
    690                 695                 700

Asn Lys Met Leu Ile Lys Asn Lys Lys Leu Lys Phe Val Lys Leu Phe
705                 710                 715                 720

Leu Ile Gln Thr Ala Ile Glu Ala Phe Arg Tyr Ala Arg Ile Phe Asn
                725                 730                 735

Gln Gln Asp Ser Phe Tyr Pro Cys Leu Gln His Phe Arg Lys Ile Lys
            740                 745                 750

Lys Arg Leu Ile Asn Lys Tyr Lys Ile Gly His Asn Lys Asn Leu Leu
        755                 760                 765

Arg Glu Phe Phe Phe Leu Phe Asn Phe Ile Lys Lys Glu Leu Tyr Asn
    770                 775                 780

Ser Trp Pro Tyr Met Phe Lys Ile Lys Asn
785                 790
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<210> 9
<211> 294
<212> DNA
<213> Oryza sativa

<220>
<221> CDS
<222> (1)..(270)
<223> Fragment of rice TERT gene

<400> 9
tta atg agg ttc att gat gat ttc ata ttt atc tct ttc tca ctg gag 48

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Leu Met Arg Phe Ile Asp Asp Phe Ile Phe Ile Ser Phe Ser Leu Glu
  1               5                  10                  15

cat gct caa aaa ttc ctc aat agg atg aga aga ggt ttt gtg ttc tac   96
His Ala Gln Lys Phe Leu Asn Arg Met Arg Arg Gly Phe Val Phe Tyr
             20                  25                  30

aat tgc tac atg aac gac agc aaa tat ggc ttt aat ttc tgt gct gga   144
Asn Cys Tyr Met Asn Asp Ser Lys Tyr Gly Phe Asn Phe Cys Ala Gly
         35                  40                  45

aat agt gag cct tcc tct aat aga ctc tac agg ggt gat gat gga gtc   192
Asn Ser Glu Pro Ser Ser Asn Arg Leu Tyr Arg Gly Asp Asp Gly Val
     50                  55                  60

tca ttc atg cca tgg agt ggt ttg cta ata aat tgt gaa act ttg gaa   240
Ser Phe Met Pro Trp Ser Gly Leu Leu Ile Asn Cys Glu Thr Leu Glu
 65                  70                  75                  80

att caa gct gat tat acg agg tat gac tgt tgaaatttgt ttttagctca     290
Ile Gln Ala Asp Tyr Thr Arg Tyr Asp Cys
                 85                  90

ttgg                                                              294


<210> 10
<211> 90
<212> PRT
<213> Oryza sativa

<400> 10
Leu Met Arg Phe Ile Asp Asp Phe Ile Phe Ile Ser Phe Ser Leu Glu
  1               5                  10                  15

His Ala Gln Lys Phe Leu Asn Arg Met Arg Arg Gly Phe Val Phe Tyr
             20                  25                  30

Asn Cys Tyr Met Asn Asp Ser Lys Tyr Gly Phe Asn Phe Cys Ala Gly
         35                  40                  45

Asn Ser Glu Pro Ser Ser Asn Arg Leu Tyr Arg Gly Asp Asp Gly Val
     50                  55                  60

Ser Phe Met Pro Trp Ser Gly Leu Leu Ile Asn Cys Glu Thr Leu Glu
 65                  70                  75                  80

Ile Gln Ala Asp Tyr Thr Arg Tyr Asp Cys
                 85                  90


<210> 11
<211> 44
<212> PRT
<213> Schizosaccharomyces pombe
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<220>
<223> T motif of TERT protein

<400> 11
Trp Leu Tyr Asn Ser Phe Ile Ile Pro Ile Leu Gln Ser Phe Phe Tyr
1 5 10 15

Ile Thr Glu Ser Ser Asp Leu Arg Asn Arg Thr Val Tyr Phe Arg Lys
20 25 30

Asp Ile Trp Lys Leu Leu Cys Arg Pro Phe Ile Thr
35 40

<210> 12
<211> 27
<212> PRT
<213> Schizosaccharomyces pombe

<220>
<223> Portion of C motif of TERT protein

<400> 12
Leu Leu Arg Val Val Asp Asp Phe Leu Phe Ile Thr Val Asn Lys Lys
1 5 10 15

Asp Ala Lys Lys Phe Leu Asn Leu Ser Leu Arg
20 25

<210> 13
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with C. albicans sequences

<400> 13
caggggtat tgaagagata gaagcagcg 29

<210> 14
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with C. albicans sequences

<400> 14
tcgttgttat tcacgcgtat cg 22

<210> 15
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer
used with C. albicans sequences

<400> 15
gcgacaattg agagatatcg ag 22

<210> 16
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer
used with C. albicans sequences

<400> 16
gcacttgatc ataaatattc gaatcggggc g 31

<210> 17
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer
used with C. albicans sequences

<400> 17
ttatggaaag agctatacg 19

<210> 18
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer
used with C. albicans sequences

<400> 18
tgagaatccc tgaaacacg 19

<210> 19
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with C. albicans sequences

<400> 19
caatttatgt gaacgcgtcc aactgagcgt ag 32

<210> 20
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with C. albicans sequences

<400> 20
gatacgacat tctatatgc 19

<210> 21
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with C. albicans sequences

<400> 21
tcaatacagg ttggctgag 19

<210> 22
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 22
tatttctgtt actcggacca 20

<210> 23
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 23
agagactcct tgttaacc 18

<210> 24
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 24
cagttaaaga tgcacgagg 19

<210> 25
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 25
tgaataacaa cagatctaag c 21

<210> 26
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 26
cagcgactgg gatggtgc 18

<210> 27
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 27
attcttgtgg tcgaatcgc 19

<210> 28
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 28
taaagcacat tgaatttgg 19

<210> 29
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencng primer

<400> 29
taaatcatcc atatgtatc 19

<210> 30
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 30
taacacgaaa gctcgagcg 19

<210> 31
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:C. albicans sequencing primer

<400> 31
aaacttatca gaccggag 18

<210> 32
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with P. falciparum sequences

<400> 32
gtcatcaata aatcggagta tgagtg 26

<210> 33
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with P. falciparum sequences

<400> 33
ttctaaccaa atctgagc 18

<210> 34
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with P. falciparum sequences

<400> 34
tgcataatat agggagcac 19

<210> 35
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with P. falciparum sequences

<400> 35
cttttgccat tctcatatga atatac 26

<210> 36
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with P. falciparum sequences

<400> 36
attattatga cgtgtgatg 19

<210> 37
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:RT-PCR primer used with P. falciparum sequences

<400> 37
catataatta catcgagg 18

<210> 38
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer for sequencing rice DNA

<220>
<221> variation
<222> (4)..(21)
<223> k at positions 4, 12, 18, 20 and 21 = g or t.

<400> 38
cctkaatatt tkttaatkak k 21

<210> 39
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer for sequencing rice DNA

<220>
<221> variation
<222> (1)..(20)
<223> k at positions 1, 11 and 20 = g or t.

<400> 39
ktcatacctc ktataatcak c 21

<210> 40
<211> 364
<212> PRT

<213> Homo sapiens

<220>
<223> Partial TERT sequence

<400> 40

```
Val Leu Leu Lys Thr His Cys Pro Leu Arg Ala Gln Leu Leu Arg Gln
  1               5                  10                  15

His Ser Ser Pro Trp Gln Val Tyr Gly Phe Val Arg Ala Cys Leu Arg
             20                  25                  30

Arg Leu Val Pro Pro Gly Leu Trp Gly Arg His Asn Glu Arg Arg Phe
         35                  40                  45

Leu Arg Asn Thr Lys Lys Phe Ile Ser Leu Gly Lys His Ala Lys Leu
     50                  55                  60

Ser Leu Gln Glu Leu Thr Trp Lys Met Ser Val Arg Ile Leu Ala Lys
 65                  70                  75                  80

Phe Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser
                 85                  90                  95

Phe Phe Tyr Val Thr Glu Thr Thr Phe Gln Lys Asn Leu Phe Phe Tyr
            100                 105                 110

Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln His
        115                 120                 125

Leu Lys Leu Arg Glu Leu Ser Glu Ala Glu Val Arg Ser Arg Leu Arg
    130                 135                 140

Phe Ile Pro Lys Pro Asp Gly Leu Arg Pro Ile Met Asn Met Asp Tyr
145                 150                 155                 160

Val Val Gly Ala Arg Thr Phe Arg Ala Glu Arg Leu Thr Ser Arg Val
                165                 170                 175

Lys Ala Leu Phe Ser Val Leu Asn Tyr Glu Ala Arg Arg Pro Gly Leu
            180                 185                 190

Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His Arg Ala Trp Arg
        195                 200                 205

Thr Phe Val Leu Arg Val Arg Pro Glu Leu Tyr Phe Val Lys Val Asp
    210                 215                 220

Val Thr Gly Ala Tyr Asp Thr Ile Pro Gln Asp Arg Leu Thr Glu Val
225                 230                 235                 240

Ile Ala Ser Ile Ile Lys Pro Gln Asn Ser Pro Leu Arg Asp Ala Val
                245                 250                 255

Val Ile Glu Gln Ser Tyr Val Gln Cys Gln Gly Ile Pro Gln Gly Ser
            260                 265                 270
```

```
Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly Asp Met Glu Asn
        275                 280                 285

Lys Leu Phe Ala Gly Ile Arg Arg Asp Leu Leu Leu Arg Leu Val Asp
    290                 295                 300

Asp Phe Leu Leu Val Thr Pro His Leu Thr His Ala Lys Thr Phe Ile
305                 310                 315                 320

Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys Val Val Asn Leu
                325                 330                 335

Arg Lys Thr Val Val Asn Phe Gln Met Pro Ala His Gly Leu Phe Pro
            340                 345                 350

Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu
        355                 360


<210> 41
<211> 364
<212> PRT
<213> Mus musculus

<220>
<223> Partial TERT sequence

<400> 41
Arg Leu Leu Arg Ser His Cys Arg Phe Arg Thr Asp Leu Leu Arg Leu
  1               5                  10                  15

His Ser Ser Pro Trp Gln Val Tyr Gly Phe Leu Arg Ala Cys Leu Cys
             20                  25                  30

Lys Val Val Ser Ala Ser Leu Trp Gly Arg His Asn Glu Arg Arg Phe
         35                  40                  45

Phe Lys Asn Leu Lys Lys Phe Ile Ser Leu Gly Lys Tyr Gly Lys Leu
     50                  55                  60

Ser Leu Gln Glu Leu Met Trp Lys Met Lys Val Glu Ile Leu Ala Thr
 65                  70                  75                  80

Phe Leu Phe Trp Leu Met Asp Thr Tyr Val Val Gln Leu Leu Arg Ser
                 85                  90                  95

Phe Phe Tyr Ile Thr Glu Ser Thr Phe Gln Lys Asn Leu Phe Phe Tyr
            100                 105                 110

Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Val Arg Gln His
        115                 120                 125

Leu Glu Leu Arg Glu Leu Ser Gln Glu Glu Val Arg Cys Arg Leu Arg
    130                 135                 140

Phe Ile Pro Lys Pro Asn Gly Leu Arg Pro Ile Met Asn Met Ser Tyr
```

```
145                 150                 155                 160

Ser Met Gly Thr Arg Ala Leu Gly Ala Gln His Phe Thr Gln Arg Leu
                165                 170                 175

Lys Thr Leu Phe Ser Met Leu Asn Tyr Glu Thr Lys His Pro His Leu
            180                 185                 190

Met Gly Ser Ser Val Leu Gly Met Asn Asp Ile Tyr Arg Thr Trp Arg
        195                 200                 205

Ala Phe Val Leu Arg Val Arg Pro Arg Met Tyr Phe Val Lys Ala Asp
    210                 215                 220

Val Thr Gly Ala Tyr Asp Ala Ile Pro Gln Gly Arg Leu Val Glu Val
225                 230                 235                 240

Val Ala Asn Met Ile Arg His Ser Glu Ser Ala Leu Arg Asn Ser Val
                245                 250                 255

Val Ile Glu Gln Ser Tyr Thr Gln Cys Gln Gly Ile Pro Gln Gly Ser
            260                 265                 270

Ser Leu Ser Thr Leu Leu Cys Ser Leu Cys Phe Gly Asp Met Glu Asn
        275                 280                 285

Lys Leu Phe Ala Glu Val Gln Arg Asp Leu Leu Leu Arg Phe Val Asp
    290                 295                 300

Asp Phe Leu Leu Val Thr Pro His Leu Asp Gln Ala Lys Thr Phe Ile
305                 310                 315                 320

Ser Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys Met Ile Asn Leu
                325                 330                 335

Gln Lys Thr Val Val Asn Phe Gln Ile Pro Ala His Cys Leu Phe Pro
            340                 345                 350

Trp Cys Gly Leu Leu Leu Asp Thr Gln Thr Leu Glu
        355                 360


<210> 42
<211> 364
<212> PRT
<213> Oxytricha trifallax

<220>
<223> Partial TERT sequence

<400> 42
Tyr Tyr Leu Ser Lys Asn Cys Pro Leu Pro Glu Gln Leu Phe Glu Tyr
  1               5                  10                  15

Gln Gln Asp Gln Arg Gln Ile Ser Asn Phe Leu Thr Glu Phe Val Ala
             20                  25                  30
```

```
Asn Val Phe Pro Lys Asn Phe Leu Glu Gly Lys Asn Lys Lys Ile Phe
          35                  40                  45

Asn Lys Lys Met Leu Gln Phe Val Lys Phe Asn Arg Phe Glu Ser Phe
      50                  55                  60

Thr Lys Ile Ser Leu Leu Asn Lys Phe Arg Val Asn Val Phe Phe Lys
 65                  70                  75                  80

Val Leu Lys Trp Met Phe Glu Asp Leu Ala Ile Thr Leu Met Arg Cys
                 85                  90                  95

Tyr Phe Tyr Ser Thr Glu Lys Ala Lys Glu Tyr Gln Leu Phe Tyr Tyr
            100                 105                 110

Arg Lys Asn Ile Trp Asn Met Ile Met Arg Leu Ser Ile Asp Asp Leu
        115                 120                 125

Leu Lys Leu Lys Gln Val Glu Lys Lys Glu Met Arg Gly Lys Leu Arg
    130                 135                 140

Leu Ile Pro Lys Gly Asp Thr Phe Arg Pro Ile Met Thr Phe Asn Arg
145                 150                 155                 160

Lys Ile Pro Asn Gln Val Gly Lys Met Thr Thr Asn Asn Lys Leu Gln
                165                 170                 175

Thr Ala His Met Met Leu Lys Asn Leu Lys Lys Met Phe Lys His Ser
            180                 185                 190

Phe Gly Phe Ala Val Phe Asn Tyr Asp Asp Ile Met Lys Arg Tyr Glu
        195                 200                 205

Asn Phe Val Gln Lys Trp Lys Pro Lys Leu Tyr Phe Val Ala Met Asp
    210                 215                 220

Ile Glu Lys Cys Tyr Asp Asn Val Asp Cys Glu Arg Val Val Asn Phe
225                 230                 235                 240

Leu Gln Lys Ser Asp Leu Met Asp Lys Leu Asn Met Lys Arg Thr Ile
                245                 250                 255

Ile Val Glu Gln Glu Tyr Arg Gln Met Lys Gly Ile Pro Gln Gly Leu
            260                 265                 270

Cys Val Ser Tyr Ile Leu Ser Ser Phe Tyr Tyr Ala Asn Leu Glu Glu
        275                 280                 285

Asn Ala Leu Gln Phe Leu Arg Lys Glu Leu Leu Met Arg Leu Thr Asp
    290                 295                 300

Asp Tyr Leu Leu Met Thr Thr Glu Lys Asn Asn Ala Met Leu Phe Ile
305                 310                 315                 320

Glu Lys Leu Tyr Gln Leu Ser Leu Gly Asn Phe Phe Lys Phe His Met
                325                 330                 335
```

```
Lys Lys Leu Lys Thr Asn Phe Asp Ser Ile Asn Asp Asp Leu Phe His
            340                 345                 350

Trp Ile Gly Ile Ser Ile Asp Ile Lys Thr Leu Asn
        355                 360


<210> 43
<211> 364
<212> PRT
<213> Euplotes aediculatus

<220>
<223> Partial TERT sequence

<400> 43
Tyr Tyr Leu Thr Lys Ser Cys Pro Leu Pro Glu Glu Leu Phe Ser Tyr
  1               5                  10                  15

Thr Thr Asp Asn Lys Cys Val Thr Gln Phe Ile Asn Glu Phe Phe Tyr
             20                  25                  30

Asn Ile Leu Pro Lys Asp Phe Leu Thr Gly Arg Asn Arg Lys Asn Phe
         35                  40                  45

Gln Lys Lys Val Lys Lys Tyr Val Glu Leu Asn Lys His Glu Leu Ile
     50                  55                  60

His Lys Asn Leu Leu Leu Glu Lys Ile Asn Thr Arg Val Leu Trp Lys
 65                  70                  75                  80

Leu Leu Arg Trp Ile Phe Phe Asp Leu Val Val Ser Leu Thr Arg Cys
                85                  90                  95

Phe Phe Tyr Met Thr Glu Gln Gln Lys Ser Tyr Ser Thr Tyr Tyr Tyr
            100                 105                 110

Arg Lys Asn Ile Trp Asp Val Ile Met Lys Met Ser Ile Ala Asp Leu
        115                 120                 125

Lys Lys Leu Ala Glu Val Gln Glu Lys Glu Val Glu Gly Lys Leu Arg
    130                 135                 140

Leu Ile Pro Lys Lys Thr Thr Phe Arg Pro Ile Met Thr Phe Asn Lys
145                 150                 155                 160

Lys Ile Val Asn Ser Asp Arg Lys Leu Thr Thr Asn Thr Lys Leu Leu
                165                 170                 175

Asn Ser His Leu Met Leu Lys Thr Leu Lys Arg Met Phe Lys Asp Pro
            180                 185                 190

Phe Gly Phe Ala Val Phe Asn Tyr Asp Asp Val Met Lys Lys Tyr Glu
        195                 200                 205

Glu Phe Val Cys Lys Trp Lys Pro Lys Leu Phe Phe Ala Thr Met Asp
```

```
    210                 215                 220

Ile Glu Lys Cys Tyr Asp Ser Val Asn Arg Glu Lys Leu Ser Thr Phe
225                 230                 235                 240

Leu Lys Thr Thr Lys Leu Leu Ser Ser Leu Asn Ala Lys Lys Thr Leu
                245                 250                 255

Ile Val Glu Ala Lys Tyr Arg Gln Thr Lys Gly Ile Pro Gln Gly Leu
            260                 265                 270

Cys Val Ser Ser Ile Leu Ser Ser Phe Tyr Tyr Ala Thr Leu Glu Glu
        275                 280                 285

Ser Ser Leu Gly Phe Leu Arg Asp Glu Leu Leu Met Arg Leu Thr Asp
    290                 295                 300

Asp Tyr Leu Leu Ile Thr Thr Gln Glu Asn Asn Ala Val Leu Phe Ile
305                 310                 315                 320

Glu Lys Leu Ile Asn Val Ser Arg Glu Asn Gly Phe Lys Phe Asn Met
                325                 330                 335

Lys Lys Leu Gln Thr Ser Phe Gln Asn Ile Val Gln Asp Tyr Cys Asp
            340                 345                 350

Trp Ile Gly Ile Ser Ile Asp Met Lys Thr Leu Ala
        355                 360
```

<210> 44
<211> 364
<212> PRT
<213> Tetrahymena thermophila

<220>
<223> Partial TERT sequence

<400> 44

```
Tyr Leu Leu Lys Lys Phe Cys Lys Leu Pro Glu Ser Leu Tyr Asp Thr
  1               5                  10                  15

Glu Ile Ser Tyr Lys Gln Ile Thr Asn Phe Leu Arg Gln Ile Ile Gln
             20                  25                  30

Asn Cys Val Pro Asn Gln Leu Leu Gly Lys Lys Asn Phe Lys Val Phe
         35                  40                  45

Leu Glu Lys Leu Tyr Glu Phe Val Gln Met Lys Arg Phe Glu Asn Gln
     50                  55                  60

Lys Val Leu Asp Tyr Ile Cys Phe Met Asp Val Phe Ile Leu Gly Asp
 65                  70                  75                  80

Leu Ile Val Phe Ile Ile Asn Lys Leu Val Ile Pro Val Leu Arg Tyr
                 85                  90                  95
```

```
Asn Phe Tyr Ile Thr Glu Lys His Lys Glu Gly Ser Ile Phe Tyr Tyr
            100                 105                 110

Arg Lys Pro Ile Trp Lys Leu Val Ser Lys Leu Thr Ile Val Lys Leu
        115                 120                 125

Glu Glu Leu Glu Lys Val Glu Glu Lys Leu Ile Pro Gly Lys Leu Arg
    130                 135                 140

Ile Ile Pro Lys Lys Gly Ser Phe Arg Pro Ile Met Thr Phe Leu Arg
145                 150                 155                 160

Lys Asp Lys Gln Lys Asn Ile Lys Leu Asn Leu Asn Gln Ile Leu Met
                165                 170                 175

Asp Ser Gln Leu Val Phe Arg Asn Leu Lys Asp Met Leu Gly Gln Lys
            180                 185                 190

Ile Gly Tyr Ser Val Phe Asp Asn Lys Gln Ile Ser Glu Lys Phe Ala
        195                 200                 205

Gln Phe Ile Glu Lys Trp Lys Pro Gln Leu Tyr Met Val Thr Leu Asp
    210                 215                 220

Ile Lys Lys Cys Tyr Asp Ser Ile Asp Gln Met Lys Leu Leu Asn Phe
225                 230                 235                 240

Phe Asn Gln Ser Asp Leu Ile Gln Asp Ser Leu Tyr Asp Asp Asp Asp
                245                 250                 255

Gln Ile Leu Gln Lys Phe Arg Gln Lys Arg Gly Ile Pro Gln Gly Leu
            260                 265                 270

Asn Ile Ser Gly Val Leu Cys Ser Phe Tyr Phe Gly Lys Leu Glu Glu
        275                 280                 285

Glu Tyr Thr Gln Phe Leu Lys Asn Ala Leu Leu Met Arg Leu Thr Asp
    290                 295                 300

Asp Tyr Leu Phe Ile Ser Asp Ser Gln Gln Asn Ala Leu Asn Leu Ile
305                 310                 315                 320

Val Gln Leu Gln Asn Cys Ala Asn Asn Asn Gly Phe Met Phe Asn Asp
                325                 330                 335

Gln Lys Ile Thr Thr Asn Phe Lys Ile Ser Val Gln Asn Glu Cys Gln
            340                 345                 350

Trp Ile Gly Lys Ser Ile Asp Met Asn Thr Leu Glu
        355                 360
```

<210> 45
<211> 364
<212> PRT
<213> Schizosaccharomyces pombe

<220>
<223> Partial TERT sequence

<400> 45

```
Lys Val Tyr Asn His Tyr Cys Pro Tyr Ile Asp Lys Ile Leu Ser Tyr
  1               5                  10                  15

Ser Leu Lys Pro Asn Gln Val Phe Ala Phe Leu Arg Ser Ile Leu Val
             20                  25                  30

Arg Val Phe Pro Lys Leu Ile Trp Gly Gln Arg Ile Phe Glu Ile Ile
         35                  40                  45

Leu Lys Asp Leu Glu Thr Phe Leu Lys Leu Ser Arg Tyr Glu Ser Phe
     50                  55                  60

Ser Leu His Tyr Leu Met Ser Asn Ile Lys Ile Ser Ile Phe Ala Glu
 65                  70                  75                  80

Phe Ile Tyr Trp Leu Tyr Asn Ser Phe Ile Ile Pro Ile Leu Gln Ser
                 85                  90                  95

Phe Phe Tyr Ile Thr Glu Ser Ser Asp Leu Arg Asn Thr Val Tyr Phe
            100                 105                 110

Arg Lys Asp Ile Trp Lys Leu Leu Cys Arg Pro Phe Ile Thr Ser Met
        115                 120                 125

Lys Met Phe Glu Lys Ile Asn Glu Asn Asn Val Arg Ala Val Ile Arg
    130                 135                 140

Leu Leu Pro Lys Lys Asn Thr Phe Arg Leu Ile Thr Asn Leu Arg Lys
145                 150                 155                 160

Arg Phe Leu Ile Lys Gln Met Gly Val Ser Thr Asn Gln Thr Leu Arg
                165                 170                 175

Pro Val Ala Ser Leu Leu Lys His Leu Ile Asn Glu Glu Ser Ser Gly
            180                 185                 190

Ile Pro Phe Asn Leu Glu Val Tyr Met Lys Leu Leu Thr Phe Lys Lys
        195                 200                 205

Asp Leu Leu Lys His Arg Met Arg Lys Lys Tyr Phe Val Arg Ile Asp
    210                 215                 220

Ile Lys Ser Cys Tyr Asp Arg Ile Lys Gln Asp Leu Met Phe Arg Ile
225                 230                 235                 240

Val Lys Lys Lys Leu Lys Asp Pro Glu Thr Leu Phe Val Asp Phe Val
                245                 250                 255

Asp Tyr Trp Thr Lys Tyr Leu Gln Lys Val Gly Ile Pro Gln Gly Ser
            260                 265                 270

Ile Leu Ser Ser Phe Leu Cys His Phe Tyr Met Glu Asp Leu Ile Asp
```

```
        275                 280                 285

Glu Tyr Leu Ser Phe Thr Lys Lys Lys Val Leu Leu Arg Val Val Asp
    290                 295                 300

Asp Phe Leu Phe Ile Thr Val Asn Lys Lys Asp Ala Lys Lys Phe Leu
305                 310                 315                 320

Asn Leu Ser Leu Arg Gly Phe Glu Lys His Asn Phe Ser Thr Ser Leu
                325                 330                 335

Glu Lys Thr Val Leu Asn Phe Phe Asn Glu Ser Lys Lys Arg Met Pro
            340                 345                 350

Phe Phe Gly Phe Ser Val Asn Met Arg Ser Leu Asp
        355                 360


<210> 46
<211> 364
<212> PRT
<213> Saccharomyces cerevisiae

<220>
<223> Partial TERT sequence

<400> 46
Ser Asp Leu Asn Ser Ile Cys Pro Pro Leu Glu Ser His Leu Ser Arg
  1               5                  10                  15

Gln Ser Pro Lys Glu Arg Val Leu Lys Phe Ile Ile Val Ile Leu Gln
            20                  25                  30

Lys Leu Leu Pro Gln Glu Met Phe Gly Lys Lys Asn Lys Gly Lys Ile
        35                  40                  45

Ile Lys Asn Leu Asn Leu Leu Leu Ser Leu Pro Leu Asn Gly Tyr Leu
    50                  55                  60

Pro Phe Asp Ser Leu Leu Lys Lys Leu Arg Leu Lys Leu Ala Ile Cys
65                  70                  75                  80

Phe Ile Ser Trp Leu Phe Arg Gln Leu Ile Pro Lys Ile Ile Gln Thr
                85                  90                  95

Phe Phe Tyr Cys Thr Glu Ile Ser Ser Thr Val Thr Ile Val Tyr Phe
            100                 105                 110

Arg His Asp Thr Trp Asn Lys Leu Ile Thr Pro Phe Ile Val Glu Tyr
        115                 120                 125

Phe Lys Leu Val Glu Asn Asn Val Cys Arg Asn His Ser Lys Met Arg
    130                 135                 140

Ile Ile Pro Lys Lys Ser Asn Phe Arg Ile Ile Ala Ile Pro Cys Arg
145                 150                 155                 160
```

```
Gly Ala Asp Glu Glu Glu Phe Thr Lys Asn Ala Ile Gln Pro Thr Gln
                165                 170                 175

Lys Ile Leu Glu Tyr Leu Arg Asn Lys Arg Pro Thr Ser Phe Thr Lys
            180                 185                 190

Ile Tyr Ser Pro Thr Gln Ile Ala Asp Arg Ile Lys Glu Phe Lys Gln
        195                 200                 205

Arg Leu Leu Lys Lys Phe Asn Pro Glu Leu Tyr Phe Met Lys Phe Asp
    210                 215                 220

Met Lys Ser Cys Tyr Asp Ser Ile Pro Arg Met Glu Cys Met Arg Thr
225                 230                 235                 240

Leu Lys Asp Ala Leu Arg Asn Glu Asn Glu Leu Tyr Ile Asp Asn Val
                245                 250                 255

Arg Thr Val His Leu Tyr Ile Arg Glu Asp Gly Leu Phe Gln Gly Ser
            260                 265                 270

Ser Leu Ser Ala Pro Ile Val Asp Leu Val Tyr Asp Asp Leu Leu Glu
        275                 280                 285

Phe Tyr Ser Glu Phe Lys Ala Ser Pro Leu Ile Leu Lys Leu Ala Asp
    290                 295                 300

Asp Phe Leu Ile Ile Ser Thr Asp Gln Gln Gln Val Ile Asn Ile Lys
305                 310                 315                 320

Lys Leu Ala Met Gly Gly Phe Gln Lys Tyr Asn Ala Lys Ala Asn Arg
                325                 330                 335

Asp Lys Ile Leu Ala Val Ser Gln Ser Asp Asp Asp Thr Val Ile Gln
            340                 345                 350

Phe Cys Ala Met His Ile Phe Val Lys Glu Leu Glu
        355                 360
```

<210> 47
<211> 379
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Consensus sequence for TERT protein

<220>
<221> VARIANT
<222> (1)..(354)
<223> X at positions 1, 5, 6, 7, 11, 13, 14, 19, 21-23, 26, 31, 34, 39, 40, 44, 62, 66, 74, 80, 92, 96, 109-113, 123, 124, 126, 129, 132, 133, 135, 137, 148, 158, 160, 168, 173, 175, 178, 181, 184, 187,

<220>
<221> VARIANT
<222> (1)..(354)
<223> cont'd.: 191, 197-203, 206, 209-211, 219, 220,
223, 227, 239, 245, 255, 256, 259, 260, 262, 265,
274, 275, 279, 302, 306, 313, 327-327, 334, 337,
342, 344-346, 354, 363, 364, 366, 369 = amino acid

<220>
<221> VARIANT
<222> (1)..(354)
<223> cont'd.: that varies according to organism

<400> 47

```
Xaa Leu Leu Lys Xaa Xaa Xaa Cys Pro Leu Xaa Glu Xaa Xaa Leu Leu
  1               5                  10                  15

Ser Tyr Xaa Ser Xaa Xaa Xaa Gln Val Xaa Asn Phe Leu Arg Xaa Ile
             20                  25                  30

Leu Xaa Lys Leu Val Pro Xaa Xaa Leu Trp Gly Xaa Arg His Asn Lys
         35                  40                  45

Lys Ile Phe Leu Lys Asn Leu Lys Lys Phe Leu Leu Xaa Lys Tyr Glu
     50                  55                  60

Xaa Leu Ser Leu Gln Glu Leu Met Xaa Lys Ile Lys Val Arg Xaa Ile
 65                  70                  75                  80

Leu Ala Lys Phe Leu Phe Trp Leu Phe Asp Xaa Leu Val Val Xaa Leu
                 85                  90                  95

Leu Arg Ser Phe Phe Tyr Ile Thr Glu Thr Thr Xaa Xaa Xaa Xaa Xaa
            100                 105                 110

Leu Phe Tyr Tyr Arg Lys Ile Trp Xaa Xaa Leu Xaa Arg Ile Xaa Phe
        115                 120                 125

Ile Xaa Xaa Leu Xaa Lys Xaa Leu Arg Glu Leu Gln Glu Lys Glu Val
    130                 135                 140

Arg Xaa Gly Lys Leu Arg Leu Ile Pro Lys Lys Xaa Thr Xaa Phe Arg
145                 150                 155                 160

Pro Ile Val Asn Met Xaa Arg Lys Val Val Xaa Arg Xaa Leu Lys Xaa
                165                 170                 175

Met Thr Xaa Asn Gln Xaa Leu Val Xaa Thr Leu Xaa Met Leu Lys Asn
            180                 185                 190

Leu Lys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Gly Xaa Ser Val Xaa Xaa
        195                 200                 205

Xaa Asp Asp Ile Met Arg Arg Trp Xaa Xaa Phe Val Xaa Lys Trp Arg
    210                 215                 220
```

```
Xaa Pro Lys Leu Tyr Phe Val Lys Val Asp Ile Lys Xaa Cys Tyr Asp
225                 230                 235                 240

Thr Ile Xaa Gln Asp Arg Leu Val Arg Val Leu Lys Xaa Xaa Ile Lys
                245                 250                 255

Xaa Xaa Glu Xaa Ser Leu Xaa Arg Asp Ser Val Val Ile Glu Gln Xaa
            260                 265                 270

Xaa Tyr Lys Gln Xaa Lys Gly Ile Pro Gln Gly Ser Ser Leu Ser Thr
        275                 280                 285

Ile Leu Cys Ser Leu Tyr Tyr Gly Asp Leu Glu Xaa Glu Glu Tyr Xaa
    290                 295                 300

Gln Phe Leu Arg Arg Asp Xaa Leu Leu Leu Arg Leu Val Asp Asp Phe
305                 310                 315                 320

Leu Leu Ile Thr Xaa Xaa Xaa Asn Asn Ala Lys Xaa Phe Leu Xaa Leu
                325                 330                 335

Leu Val Arg Xaa Gly Xaa Xaa Xaa Tyr Gly Phe Lys Val Asn Leu Xaa
            340                 345                 350

Lys Thr Val Val Asn Phe Gln Met Xaa Xaa His Xaa Leu Met Xaa Trp
        355                 360                 365

Ile Gly Leu Ser Ile Asp Ile Arg Thr Leu Glu
    370                 375
```

<210> 48
<211> 271
<212> DNA
<213> Arabidopsis thaliana

<220>
<223> Segment of TERT gene

<400> 48
ttactgagat ttattgatga ctacattttt gtgtctacct caagagatca ggcgagtagc 60
ttctatcaca ggttgaagca tggatttaaa gattacaact gcttcatgaa cgaaacaaaa 120
ttctgcataa attttgaaga taaagaagaa cataggtgtt cttataatag aatgtttgtg 180
ggcgataatg gagttccttt tgtcagatgg acgggtttgc ttattaattc ccgcacattt 240
gaagttcaag ttgactacac aaggtctgcc t 271